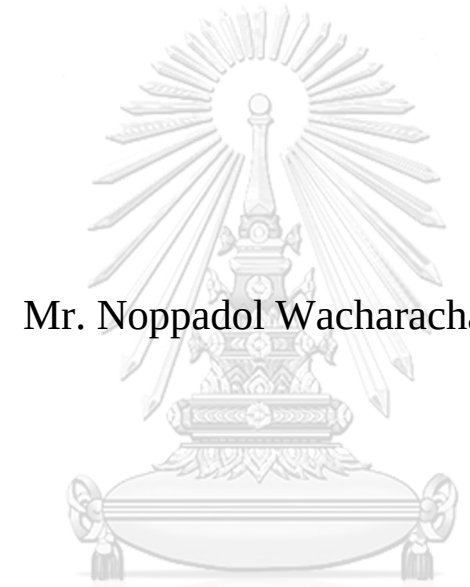
POPULATION PHARMACOKINETICS OF INTRAVENOUS COLISTIN IN PEDIATRICS (POPPICOP study)

Mr. Noppadol Wacharachaisurapol



A Dissertation Submitted in Partial Fulfillment of the Requirements
for the Degree of Doctor of Philosophy in Clinical Sciences
Common Course
FACULTY OF MEDICINE
Chulalongkorn University
Academic Year 2020

การศึกษาเภสัชจลนศาสตร์ประชากรของยาโคลิสตินชนิดฉีดเข้าหลอดเลือดดำในผู้ป่วยเด็ก

นายนพดล วัชระชัยสุรพล

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรดุษฎีบัณฑิต
สาขาวิชาเวชศาสตร์คลินิก ไม่สังกัดภาควิชา/เทียบเท่า
คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
ปีการศึกษา 2563

Thesis Title	POPULATION PHARMACOKINETICS OF INTRAVENOUS COLISTIN IN PEDIATRICS (POPPICOP study)
By	Mr. Noppadol Wacharachaisurapol
Field of Study	Clinical Sciences
Thesis Advisor	Associate Professor THANYAWEE PUTHANAKIT, M.D.
Thesis Co Advisor	Assistant Professor Thitima Wattanavijitkul, Ph.D. Associate Professor WARUNEE PUNPANICH VANDEPITTE, M.D., Ph.D.

Accepted by the FACULTY OF MEDICINE, Chulalongkorn University in Partial Fulfillment of the Requirement for the Doctor of Philosophy

..... Dean of the FACULTY OF MEDICINE
(Professor SUTTIPONG WACHARASINDHU, M.D.)

DISSERTATION COMMITTEE

..... Chairman
(Assistant Professor OPASS PUTCHAROEN, M.D.)
..... Thesis Advisor
(Associate Professor THANYAWEE PUTHANAKIT, M.D.)
..... Thesis Co-Advisor
(Assistant Professor Thitima Wattanavijitkul, Ph.D.)
..... Thesis Co-Advisor
(Associate Professor WARUNEE PUNPANICH VANDEPITTE, M.D., Ph.D.)
..... Examiner
(Assistant Professor Pajaree Chariyavilaskul, M.D., Ph.D.)
..... Examiner
(Assistant Professor ANKANEE CHANAKUL, M.D.)
..... External Examiner
(Associate Professor Preecha Montakantikul, BCPS)

นพดล วัชระชัยสุรพล : การศึกษาเภสัชจลนศาสตร์ประชากรของยาโคลิสตินชนิดฉีดเข้าหลอดเลือดดำในผู้ป่วยเด็ก. (POPULATION PHARMACOKINETICS OF INTRAVENOUS COLISTIN IN PEDIATRICS (POPPICOP study)) อ.ที่ปรึกษาหลัก : รศ. พญ.ธันยวีร์ ภูธนกิจ, อ.ที่ปรึกษาร่วม : ผศ. ดร.ธิติมา วัฒนวิจิตรกุล,รศ. พญ.วารุณี พรรณพานิช วานเดอพิทท์

ที่มาและความสำคัญ: ปริมาณการใช้ยาโคลิสตินในผู้ป่วยเด็กเพิ่มสูงขึ้นตามปัญหาเชื้อแบคทีเรียกรัมลบดื้อยาที่ทวีความรุนแรงมากขึ้น อย่างไรก็ตาม ขนาดยาโคลิสตินที่เหมาะสมในเด็กยังไม่เป็นที่ทราบแน่ชัดเนื่องจากขาดข้อมูลที่สำคัญด้านเภสัชจลนศาสตร์ การศึกษานี้มีวัตถุประสงค์เพื่อศึกษาลักษณะทางเภสัชจลนศาสตร์ประชากรของยาโคลิสตินชนิดฉีดเข้าหลอดเลือดดำในผู้ป่วยเด็ก หาปัจจัยที่มีผลต่อค่าพารามิเตอร์ทางเภสัชจลนศาสตร์ และแนะนำขนาดยาและวิธีการบริหารยาที่เหมาะสม

วิธีวิจัย: การศึกษานี้เป็นการศึกษาเภสัชจลนศาสตร์ประชากรแบบไปข้างหน้าและมีหลายศูนย์วิจัย ตัวอย่างเลือดจะถูกเก็บจากผู้ป่วยหลังจากได้รับยาโคลิสตินขนาดมาตรฐานที่แนะนำในปัจจุบันคือ 5 มก./กก./วัน และวัดระดับยาโคลิสตินในพลาสมา ข้อมูลระดับยาในเลือดจะได้มาจากการศึกษานี้ร่วมกับการศึกษาก่อนหน้า เพื่อใช้ในการวิเคราะห์ทางเภสัชจลนศาสตร์ประชากร สร้างแบบจำลองทางเภสัชจลนศาสตร์ประชากรที่ใช้ประมาณค่าและหาปัจจัยที่มีผลต่อค่าพารามิเตอร์ทางเภสัชจลนศาสตร์ด้วยโปรแกรม Phoenix™ 64 version 8.3 แบบจำลองเภสัชจลนศาสตร์ประชากรที่ได้จะถูกประเมินความถูกต้องด้วยกระบวนการต่าง ๆ ได้แก่ goodness-of-fit plots, bootstrap analysis, และ prediction corrected-visual predictive check จากนั้นจะทำการจำลองสถานการณ์เพื่อหาขนาดยาโคลิสตินที่เหมาะสม

ผลการวิจัย: ระหว่างเดือนมีนาคม พ.ศ. 2561 ถึง กุมภาพันธ์ พ.ศ. 2564 มีผู้ป่วยเข้าร่วมโครงการวิจัย 59 ราย (ตัวอย่างเลือด 187 ตัวอย่าง) ร่วมกับข้อมูลของผู้ป่วย 20 ราย (ตัวอย่างเลือด 147 ตัวอย่าง) จากการศึกษาก่อนหน้า รวมเป็นตัวอย่างเลือดระดับยาโคลิสตินในพลาสมาทั้งหมด 334 ตัวอย่างจากผู้ป่วยเด็ก 79 รายที่มีค่ามัธยฐานของอายุ 2.6 ปี (0.8-6.8) อธิบายได้ด้วยแบบจำลองที่มีลักษณะทางเภสัชจลนศาสตร์แบบหนึ่งห้องและมีการกำจัดยาแปรผันตรงกับความเข้มข้นของยาโดยมีระดับครีอะตินินเป็นปัจจัยที่ส่งผลกระทบต่ออัตราการกำจัดยา อัตราการกำจัดยาโคลิสตินเท่ากับ 0.069 ลิตร/ชม.*กก. การกระจายยาเท่ากับ 0.658 ลิตร/กก. จากแบบจำลองพบว่าขนาดยาที่แนะนำ ได้แก่ 5 มก./กก./วัน ทำให้ระดับยาเฉลี่ยที่ภาวะคงที่ถึงเป้าหมายที่ต้องการ (2 มก./ลิตร) ร้อยละ 18.2 ถึง 30.1 และ 40.2 ถึง 63.0 ของผู้ป่วยจำลองที่มีระดับครีอะตินิน 0.1 ถึง 0.3 และ 0.31 ถึง 0.75 ตามลำดับ เมื่อระดับยาเฉลี่ยที่ภาวะคงที่ที่ต้องการเท่ากับ 1 มก./ลิตร ร้อยละ 61.1 ถึง 75.0 และ 82.6 ถึง93.6 ของผู้ป่วยจำลองที่มีระดับครีอะตินิน 0.1 ถึง 0.3 และ 0.31 ถึง 0.75 ตามลำดับ จะมีระดับยาถึงเป้าหมายที่ต้องการ

สรุปผล: ค่าครีอะตินินเป็นปัจจัยสำคัญที่ส่งผลกระทบต่ออัตราการกำจัดยาโคลิสตินในผู้ป่วยเด็ก ผู้ป่วยที่มีค่าครีอะตินินต่ำกว่า ต้องการขนาดยาโคลิสตินที่สูงกว่าและมักสูงกว่าขนาดยาที่แนะนำไว้ในปัจจุบัน ทั้งนี้เนื่องจากมีการกำจัดยาออกจากร่างกายมากกว่า

สาขาวิชา	เวชศาสตร์คลินิก	ลายมือชื่อนิสิต .....
ปีการศึกษา	2563	ลายมือชื่อ อ.ที่ปรึกษาหลัก .....
		ลายมือชื่อ อ.ที่ปรึกษาร่วม .....
		ลายมือชื่อ อ.ที่ปรึกษาร่วม .....

5974858630 : MAJOR CLINICAL SCIENCES
KEYWORD: colistin, population pharmacokinetics, pediatrics, multidrug-resistant Gram-negative bacteria

Noppadol Wacharachaisurapol : POPULATION PHARMACOKINETICS OF INTRAVENOUS COLISTIN IN PEDIATRICS (POPPICOP study). Advisor: Assoc. Prof. THANYAWEE PUTHANAKIT, M.D. Co-advisor: Asst. Prof. Thitima Wattanavijitkul, Ph.D.,Assoc. Prof. WARUNEE PUNPANICH VANDEPITTE, M.D., Ph.D.

Background: Colistin use in pediatrics is surging in line with the increase of multidrug-resistant Gram-negative bacteria (MDR-GNB). However, the appropriate dose is uncertain owing to the lack of pharmacokinetics data. In this study, we aimed to characterize the pharmacokinetic parameters of colistin in pediatric patients, identify the factors influencing the pharmacokinetic parameters, and propose optimal dosage regimens.

Methods: A prospective, multicenter, population pharmacokinetic (PPK) study was conducted. Serial blood samples were obtained from patients after receiving the standard colistin recommended dose of 5 mg of colistin base activity (CBA)/kg/day. Plasma colistin concentrations were measured. Data were pooled from this study and the previous study to create a data set for PPK analysis. A PPK model was performed with the Phoenix^{TM} 64 version 8.3. The final model was evaluated by goodness-of-fit plots, bootstrap analysis, and prediction corrected-visual predictive check. Simulation using the final PPK model was done to propose optimal colistin dosage regimens.

Results: From March 2018 to February 2021, 59 patients (187 plasma samples) were enrolled. Data were pooled with 20 patients (147 plasma samples) from the previous study. A total of 334 plasma colistin concentrations from 79 pediatric patients with a median age (IQR) of 2.6 years (0.8-6.8) were adequately described by a one-compartment model with first-order elimination along with serum creatinine (SCr) as a significant covariate on colistin clearance (CL). Colistin CL was 0.069 L/h*kg, the volume of distribution (V) was 0.658 L/kg. Model-based simulation demonstrated that with the recommended dose of 5 mg of CBA/kg/day, the probability target attainment (PTA) was 18.2-30.1% and 40.2-63.0% in the patients with a SCr level of 0.1-0.3 mg/dL and 0.31-0.75 mg/dL, respectively when the target plasma colistin average steady-state concentration ($C_{ss,avg}$) was 2 mg/L. For a lower target $C_{ss,avg}$ of 1 mg/L, PTA was 61.1–75.0% and 82.6–93.6% in the patients with a SCr level of 0.1-0.3 mg/dL and 0.31-0.75 mg/dL, respectively.

Conclusions: SCr is a significant covariate on colistin clearance in pediatric patients. Patients with a lower SCr level require a higher dose of colistin, especially higher than the current recommendation, owing to the increase of colistin elimination.

Field of Study: Clinical Sciences
Academic Year: 2020

Student's Signature .....
Advisor's Signature .....
Co-advisor's Signature .....
Co-advisor's Signature .....

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude for all contributions to this work. Foremost, my advisor Assoc. Prof. Thanyawee Puthanakit for the continuous support of my Ph.D. study and research, for her patience, motivation, and immense knowledge. Her guidance helped me in all the time of research and writing of this thesis. She is also a great role model for being a good researcher and teacher. I could not have imagined having a better advisor and mentor for my Ph.D. study.

Besides my advisor, I would like to thank my thesis co-advisors: Asst. Prof. Thitima Wattanavijitkul who helped and guided me on performing population PK analysis which is one of the most difficult steps in this thesis with her kindness; Assoc. Prof. Warunee Punpanich Vandepitte who offered me a chance to conduct this research at Queen Sirikit National Institute of Child Health and made this research be a multicenter study. My sincere thanks also go to the rest of my thesis committee: Asst. Prof. Opass Putcharoen; Asst. Prof. Pajaree Chariyavilaskul; Asst. Prof. Ankanee Chanakul; and Assoc. Prof. Preecha Montakantikul for their encouragement and insightful comments. I am also grateful to acknowledge Professor Emeritus Dwip Kitayaporn; Prof. Wasee Tulvatana; all instructors of Clinical Sciences (International Program) for their valuable suggestions.

I also would like to thank Dr. Prawat Chantharit for his guidance and help in verifying the population PK analysis and simulations, all study teams including QSNICH PICU, Center of Excellence for Pediatric Infectious Diseases and Vaccines, Chula Clinical Research Laboratory (CRL)/HIV-NAT AIDS Research Laboratory, Clinical Pharmacokinetics and Pharmacogenomics Research Unit, those who contributed in this study and their names have not been mentioned, and most importantly, all patients and their families that made this study successfully finished.

I am grateful to acknowledge the scholarship from “The 100th Anniversary Chulalongkorn University Fund for Doctoral Scholarship” and “The 90th Anniversary Chulalongkorn University Fund (Ratchadaphiseksomphot Endowment Fund)”.

Lastly, I would like to thank my family for all kinds of support throughout the Ph.D. study period and my life.

Noppadol Wacharachaisurapol

TABLE OF CONTENTS

Page

..... iii

ABSTRACT (THAI) iii

.....iv

ABSTRACT (ENGLISH).....iv

ACKNOWLEDGEMENTS.....v

TABLE OF CONTENTS.....vi

LIST OF TABLES.....ix

LIST OF FIGURES x

LIST OF ABBREVIATIONS.....11

CHAPTER I INTRODUCTION.....13

1.1. Background and rationale 13

1.2. Objectives 14

1.2.1. Primary objective 14

1.2.2. Secondary objectives.....14

CHAPTER II LITERATURE REVIEW 15

2.1. Colistin.....15

2.1.1. Physicochemical properties.....15

2.1.2. Mechanism of action 16

2.1.3. Pharmacokinetics.....16

2.1.4. Possible covariates on colistin pharmacokinetics 21

2.1.5. Pharmacodynamics.....24

2.1.6. Clinical uses 25

2.1.7. Adverse drug reactions.....25

2.1.8. Colistin determination 28

2.2. Population pharmacokinetics by using nonlinear mixed-effects models approach 29

2.2.1. Background 29
2.2.2. Model development 30
2.2.3. Model evaluation 31
2.3. Monte Carlo simulation for pharmacodynamic assessment 32
CHAPTER III METHODOLOGY 34
3.1. Study design 36
3.2. Patients and methods 36
3.2.1. Population and samples 36
3.2.2. Data collection 37
3.2.3. Recommended dose of colistin 37
3.2.4. Blood sampling 38
3.2.5. Determination of colistin concentration in plasma 39
3.2.6. Population pharmacokinetic analysis and simulation 40
3.2.7. Pharmacodynamic assessment using simulation 42
3.2.8. Statistical analysis 42
3.3. Study outcomes 43
3.3.1. The primary outcome 43
3.3.2. The Secondary outcomes 43
3.4. Ethical considerations 43
CHAPTER IV RESULTS 44
4.1. Demographic and clinical data 44
4.1.1. Patient demographics 44
4.1.2. Colistin administration 44
4.1.3. Microbiological data 44
4.1.4. The association of giving an intravenous colistin loading dose and rates of AKI 47
4.2. Population pharmacokinetic analysis 49
4.2.1. Base model 49
4.2.2. Covariate model and final model 54

4.2.3. Model evaluation 58
4.3. Pharmacodynamic assessment using simulation 59
CHAPTER V DISCUSSION 62
Appendix A: The methodology of study 3 (No Increased Acute Kidney Injury Rate Through Giving an Intravenous Colistin Loading Dose in Pediatric Patients) 70
Appendix B: Colistin package inserts 73
Appendix C: Validation of LC-MS/MS method for colistin determination 76
Appendix D: Ethical approvals 79
Appendix E: Worksheet using for simulations. 82
Appendix F: Codes for model simulations. 83
Appendix G: Published manuscript entitled " No Increased Acute Kidney Injury Rate Through Giving an Intravenous Colistin Loading Dose in Pediatric Patients" 84
Appendix H: Accepted manuscript entitled "Dose recommendations for intravenous colistin in pediatric patients from a prospective, multicenter, population pharmacokinetic study" 91
REFERENCES 112
VITA 119

LIST OF TABLES

Page

Table 1. PK parameters of formed colistin from traditional PK studies with non-compartmental model analysis. 19

Table 2. Summary of estimated PK parameters and significant covariates of formed colistin from population pharmacokinetic studies. 20

Table 3. Daily doses of colistin methanesulfonate (CMS) in adults for a desired target colistin $C_{ss,avg}$ of 2 mg/L for narrow windows of creatinine clearance. 22

Table 4. Reference values of serum creatinine in children. 23

Table 5. Comparison of characteristics and reported nephrotoxicity rate among studies of critically ill pediatric patients receiving intravenous colistin. 27

Table 6. Comparison of traditional and population pharmacokinetics. 30

Table 7. Scope and characteristics of three studies on intravenous colistin in pediatric patients. 35

Table 8. Blood sampling schedule varied by colistin administration intervals. 39

Table 9. Patient demographics. 45

Table 10. Median baseline serum creatinine classified by age groups. 46

Table 11. Association of characteristics of pediatric patients without impaired kidney function at baseline administered with intravenous colistin and acute kidney injury. 48

Table 12. The comparisons of -2LL, AIC, BIC, and population pharmacokinetic parameter estimates in the residual error model selection process. 51

Table 13. Forward addition and backward elimination steps of covariate model development. 56

Table 14. Evalulation of covariance model. 57

Table 15. Population pharmacokinetic parameter estimates of the final model and bootstrap. 57

Table 16. Probability of target attainment of simulated patients with different serum creatinine levels who achieved target $C_{ss,avg}$ at different colistin dosing regimens (N = 10,000 replicates per clinical scenario). 61

LIST OF FIGURES

Page

Figure 1. The Structure of colistin A and B and colistin methanesulfonate.....15

Figure 2. Overview of elimination pathways of CMS and colistin after CMS intravenous administration. 17

Figure 3. Blood sampling stratification. 39

Figure 4. Plasma colistin concentrations versus time profile of pediatric patients after receiving intravenous colistin. 49

Figure 5. Plasma colistin concentrations versus time profile of 20 patients after administering the first dose of colistin. 50

Figure 6. Goodness-of-fit plots for the structural model. 50

Figure 7. Goodness-of-fit plots (DV versus IPRED or PRED) for the base model and the final model. 52

Figure 8. oodness-of-fit plots (CWRES versus PRED or TAD) for the base model and the final model.....53

Figure 9. Scatterplots of the relationship between individual covariate values and random effect of drug clearance and volume of distribution during the covariate search process. 55

Figure 10. Prediction corrected-visual predictive check of the final model. 59

LIST OF ABBREVIATIONS

Abbreviation	Meaning
-2LL	Twice negative log-likelihood
ADR	Adverse drug reaction
AIC	Akaike information criterion
AKI	Acute kidney injury
Alb	Serum albumin
AUC	Area under the curve
BIC	Bayesian information criterion
BUN	Blood urea nitrogen
CBA	Colistin base activity
CI	Confidence interval
CL	Apparent clearance of the drug
CLABSI	Central line-associated bloodstream infection
CLSI	Clinical & Laboratory Standards Institute
Cmax	Maximum concentration in plasma
CMS	Colistin methanesulfonate
CRBSI	Catheter-related bloodstream infection
CrCl	Creatinine clearance
CRE	Carbapenem-resistant Enterobacteriaceae
$C_{ss,avg}$	Plasma colistin average steady-state concentration
CWRES	Conditional weighted residuals
DV	Observed concentration
ECMO	Extracorporeal membrane oxygenation
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
*f*AUC	The unbound colistin concentration in plasma
HPLC	High performance liquid chromatography
IIV	Interindividual variability
IPRED	Individual-predicted concentration

Abbreviation	Meaning
IQR	Interquartile range
IWRES	Individual weighted residuals
KCMH	King Chulalongkorn Memorial Hospital
KDIGO	The Kidney Disease: Improving Global Outcomes
LC-MS/MS	Liquid chromatography-tandem mass spectometry
LPS	Lipopolysaccharide
MDR-GNB	Multidrug-resistant Gram-negative bacteria
MIC	Minimum inhibitory concentration
NCA	Non-compartmental analysis
NLME	Nonlinear mixed effects
OFV	Objective function value
pcVPC	Prediction-corrected visual predictive check
PD	Pharmacodynamic
PK	Pharmacokinetic
PPK	Population pharmacokinetic
PRED	Population-predicted concentration
PTA	Probability of target attainment
QSNICH	Queen Sirikit National Institute of Child Health
RRT	Renal replacement therapy
RV	Residual variability
SCr	Serum creatinine
TAD	Time after dose
TDM	Therapeutic drug monitoring
US FDA	United States Food and Drug Administration
V	Volume of distribution
VPC	Visual predictive check

CHAPTER I INTRODUCTION

1.1. Background and rationale

Multidrug-resistant Gram-negative bacteria (MDR-GNB) is a global health threat and the burden of infectious diseases from MDR-GNB is increasing rapidly [1, 2]. According to the high burden of MDR bacteria and the lack of new antibiotics for combating these organisms, the World Health Organization stated a global priority pathogens list of antibiotic-resistant bacteria On February 2017 [3]. The critical priority including carbapenem-resistant *Acinetobacter baumannii*, carbapenem-resistant *Pseudomonas aeruginosa*, 3rd generation cephalosporin-resistant, or carbapenem-resistant Enterobacteriaceae (CRE). Data from National Antimicrobial Resistance Surveillance Center, Thailand (NARST) 2000-2020 [4] clearly shows an increase of the carbapenem-resistant rate of GNB; *Acinetobacter* spp. from 5.8% to 72.5%; *P. aeruginosa* from 10.7% to 21.5%; *Klebsiella pneumoniae* from 1% to 10.5%. Data from the antibiogram of King Chulalongkorn Memorial Hospital (KCMH) 2019 shows similar carbapenem-resistant rates of *A. baumannii* (85%) and *P. aeruginosa* (25%), but 2 times higher rate of CRE (20%).

Pediatric patients who are infected with MDR-GNB require complex antibiotic regimens, longer hospitalization, and more likely to have higher morbidity and mortality [1]. Kapoor K et al. (2013) [5] found that the most common MDR-GNB in a pediatric intensive care unit (PICU) were also *A. baumannii* (64%), Enterobacteriaceae (20%), and *P. aeruginosa* (16%). The mortality rate was as high as 28%. One of the last resorts for the treatment of these carbapenem-resistant Gram-negative bacteria is colistin.

Colistin or polymyxin E, discovered in 1949 in Japan, is a polypeptide antibiotic with concentration-dependent killing activity. At the high plasma concentration, colistin will act as a bactericidal drug whereas, at the low plasma concentration, colistin will act as a bacteriostatic drug. The mechanism of action comes from the positive charges of polypeptide chains that interact with the negative charges of lipopolysaccharide at the bacterial cell membrane. This interaction causes cell membrane instability and bacterial cell lysis. The use of this antibiotic had been

inflating for almost 20 years (the 1960s to early 1970s). Afterward, colistin use declined rapidly according to the possible serious adverse reactions (nephrotoxicity and neurotoxicity). Recently, colistin has been bringing back for the treatment of MDR-GNB infections that is resistant to many classes of antibiotics including carbapenems but susceptible to colistin [6]. At present, the available formulations of colistin are colistimethate sodium, so-called colistin methanesulfonate (CMS), and colistin sulfate. CMS is a prodrug of colistin used as a parenteral route and will be hydrolyzed to active metabolites (formed colistin A and B) while colistin sulfate is for enteral or topical use [2]. The dosing of CMS is usually described as “milligram of colistin base activity (CBA)” or “International Units (IU)”. One mg of CBA (30,000 IU) is equal to 2.4 mg of CMS [7].

Colistin is an ancient antibiotic discovered in the period that the pharmacokinetic (PK) study is limited. In the past ten years, pharmacokinetic studies of colistin in adults were published. The knowledge gained resulted in the dose recommendations in adults in various populations. However, the dosing of colistin in pediatric patients is problematic owing to the lack of pharmacokinetics knowledge in this specific population. Pharmacokinetic study of colistin in this particular population is urgently needed to guide pediatricians for the appropriate dose of this life-saving drug.

1.2. Objectives

1.2.1. Primary objective

- To describe the population PK parameters of formed colistin (colistin A, B) in pediatric patients and to identify the covariate(s) influencing the PK parameters.

1.2.2. Secondary objectives

- To suggest the appropriate regimen of intravenous colistin regarding the significant covariate(s).

To describe the rate of acute kidney injury which is the most common adverse drug reaction of colistin.

CHAPTER II LITERATURE REVIEW

2.1. Colistin

2.1.1. Physicochemical properties [8]

Colistin is a polypeptide antibiotic with a structure of a cyclic heptapeptide and a tripeptide side chain attached with a fatty acid at the N-terminus by acetylation. Two major components are colistin A (polymyxin E1) and B (polymyxin E2). The difference between colistin A and B is the fatty acid; 6-methyloctanoic acid for colistin A and 6-methylheptanoic acid for colistin B. The parenteral formulation of colistin is CMS. CMS is a prodrug of colistin synthesized by the reaction of colistin with formaldehyde followed by sodium bisulfite. From this reaction, the sulfomethyl groups were added to the primary amines of colistin (Figure 1).

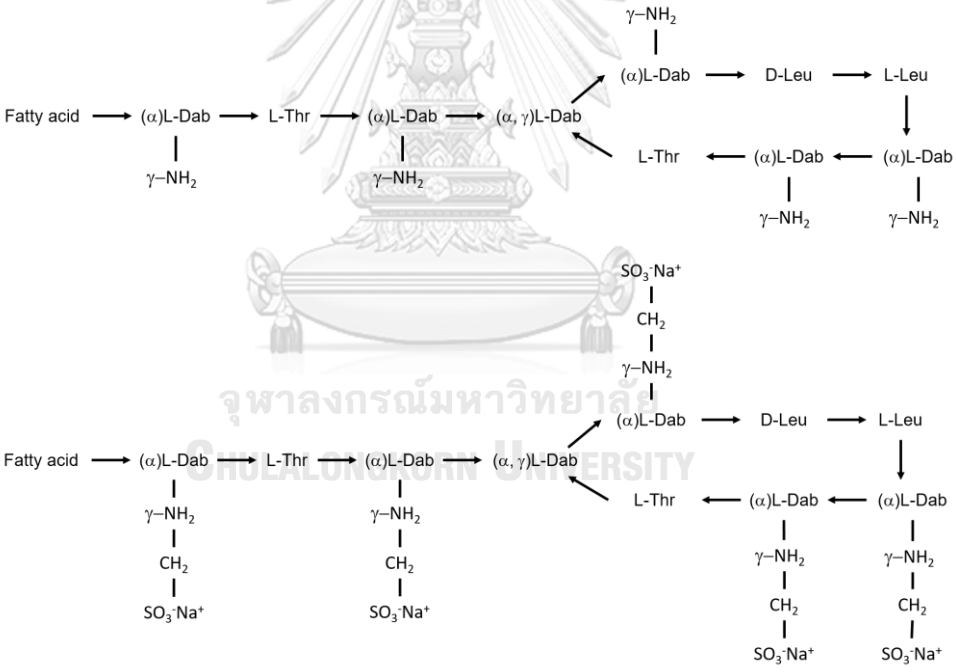


Figure 1. The Structure of colistin A and B and colistin methanesulfonate.
(A) colistin A and B, (B) colistin methanesulfonate. The fatty acid of colistin A is 6-methyloctanoic acid; colistin B is 6-methylheptanoic acid. Thr, threonine; Leu, leucine; Dab, α,γ-diaminobutyric acid. α and γ indicate the respective amino group involved in the peptide linkage. Modified from Li J et al. [9]

2.1.2. Mechanism of action

Colistin is an antibiotic with bactericidal activity. Regarding the structure of colistin in physiological pH in plasma, colistin has a polycationic status and acts as a detergent on the bacterial cell membrane. The interactions between colistin and anionic lipopolysaccharide (LPS) molecules in the outer membrane of Gram-negative bacteria causes derangement of the cell membrane. Colistin also displaces magnesium (Mg^{2+}) and calcium (Ca^{2+}) in the LPS molecules causing the instability of these structures. The result of this process causes an increase in the permeability of the cell envelope, leakage of cell contents, and, subsequently, cell death [9, 10].

2.1.3. Pharmacokinetics

2.1.3.1. ADME summary

Almost all of the available data were from adult PK studies. The summary of ADME is as follows:

- Absorption: CMS is not absorbed via the gastrointestinal tract but well absorbed via intramuscular injection [10].
- Distribution: Colistin protein binding in adults and children is similar at 50% and 53%, respectively [11, 12]. Colistin is poorly distributed to the lung parenchyma, pleural fluid, and central nervous system. An adult study measured colistin in bronchoalveolar lavage (BAL) fluid after administering CMS 220 mg of CBA/day. Colistin was undetectable [13]. A pediatric study reported that colistin penetration into the cerebrospinal fluid was minimal (<0.2 mg/L) [14].
- Metabolism: After administering CMS into the body, CMS will be hydrolyzed by esterases in plasma [15] to form a complex mixture of colistin, mainly is colistin A and B, and as well as sulfomethylated derivatives. In an in vitro study, 31.2% of CMS in human plasma was hydrolyzed to colistin in 4 h at 37 °C [10]. This proportion of CMS metabolism is similar to a recent study showing that 30% of CMS was hydrolyzed to colistin [16].

- Excretion: CMS is primarily (60%) excreted unchanged via glomerular filtration. There is no report about biliary excretion. Formed colistin is mainly eliminated from the body by non-renal mechanisms that are not yet fully characterized. In patients with renal impairment, CMS dose should be decreased regarding the decreased renal clearance of CMS and a greater fraction of plasma CMS would be converted to colistin [9]. The proposed elimination pathways of CMS and colistin are shown in Figure 2.

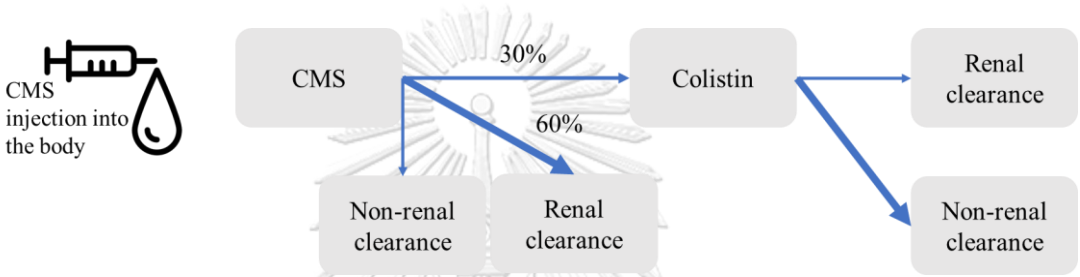


Figure 2. Overview of elimination pathways of CMS and colistin after CMS intravenous administration.
CMS, colistin methanesulfonate. The thickness of arrows stated the magnitude of the clearance pathways. Modified from Li J et al. [9].

2.1.3.2. Adult pharmacokinetic studies

Currently, there are PK studies in various adult populations. According to the heterogeneity of studies, comparison between studies is challenging. PK parameters of formed colistin from traditional (full) pharmacokinetics by a non-compartmental analysis (NCA) are shown in Table 1. According to the limitations of traditional PK study such as intensive blood samplings, strict blood sampling schedule, population pharmacokinetic (PPK) studies were conducted among various kinds of participants. A summary of clinical characteristics and estimated PK parameters from PPK studies are shown in Table 2. Suggestions for colistin dosing from adult studies are as follows:

- A loading dose is essential especially in critically ill patients [17-20].
- Loading dose could be calculated from target plasma colistin average steady-state concentration ($C_{ss,avg}$) × 2.0 × body weight (kg) when

colistin $C_{ss,avg}$ is the average concentration at the steady-state. The desired level is at least 2 mg/L [21].

- The first maintenance dose should be administered 12 h after the loading dose [17].
- A higher maintenance dose would be required for patients with creatinine clearance of >80 mL/min/1.73 m^2 [17].

Table 1. PK parameters of formed colistin from traditional PK studies with non-compartmental model analysis.

Study	N	Subject	Age (year)	Colistin dose[a]	C_{max} (mg/L)	T_{max} (h)	t1/2 (h)	V (L/kg)	CL (L/h/kg)
Adult studies									
Mizuyachi et al., 2011 [22]	15	Healthy adults	28.0 ± 3.6[c]	2.5 mg/kg q 12 h	4.4 ± 1.6	2 (1–4)	4.98 ± 0.99	1.0 ± 0.2	0.15
Karnik et al., 2013 [23]	15	Critically ill	15–40	130–200 mg/day	4.6 (2.5–23.2)[c]	0.5	2.7 (1.1–4.6)[c]	0.3 (0.2–0.5)[d]	0.07
				1.7 mg/kg/day (decreaed CrCl)	5.4 (1.8–21.8)[c]	0.5	3.3 (1.2–5.4)[c]	0.3 (0.2–0.5)[d]	0.07
Moni et al., 2020 [24]	19	Critically ill	55 ± 13.5	270 mg loading, 270 mg/day maintenance	2.4 ± 1.4[c]	2.5 ± 2.5[c]	NA	9.9 ± 4.8[c]	NA
Neonatal study									
Nakwan et al., 2016 [15]	7	Critically ill neonates	13 days (5–15)[d]	5	3.0 ± 0.7[c]	1.3 ± 0.9[c]	9.0 ± 6.5[c]	7.7 ± 9.3[c]	0.6 ± 0.3[c]
Pediatric study									
Wacharachaisurapol et al., 2020 [25]	20	Critically ill children	8.5 (3.5–11.3)[d]	4 mg/kg	6.1 ± 2.4[c]	2.5 ± 0.6[c]	2.9 ± 0.6[c]	0.7 ± 0.4[c]	0.2 ± 0.1[c]
				1.7 or 2.5 mg/kg	4.1 ± 1.3[c]	2.7 ± 0.5[c]	2.6 ± 0.4[c]	0.6 ± 0.3[c]	0.2 ± 0.1[c]

CL, drug clearance; CrCl, creatinine clearance; C_{max}, maximum concentration, T_{max}, time to C_{max}; t1/2, half-life; NA, not available; V, volume of distribution.

[a]mg of CBA, [b]mean (range), [c]mean ± SD, [d]median (range).

Table 2. Summary of estimated PK parameters and significant covariates of formed colistin from population pharmacokinetic studies.

Study	N	Subject	V (L)	CL (L/h)	Covariate tested	Significant covariates
Adult studies						
Plachouras et al., 2009 [18]	18	Critically ill	189	9.1	BW, IBW, age, CrCl, Hb, Hct	None
Garonzik et al., 2011 [21]	105	Critically ill including 12 with intermittent HD and 4 with CRRT	45.1	2.7	Actual BW, IBW, BSA, BMI, gender, age, CrCl, and APACHE II score on clearance Actual BW, IBW, BSA, BMI on volume of distribution	CrCl (↑) on CL (↑)
Mohamed et al., 2012 [19]	10	Critically ill	218	8.2	BW, IBW, gender, age, serum creatinine, CrCl, serum albumin, Hb, Hct, septicemic state, APACHE II score	None
Grégoire et al., 2014 [26]	73	Critically ill	10.2	2.3	BW, gender, age, simplified acute physiology score (SAPS II), BT, CrCl, diuresis, urinary pH, blood pH, Hb and other blood chemistries	BT (↑) on V (↓), BUN (↑) on CL (↓)
Karaiskos et al., 2015 [27]	19	Critically ill	80.4	4.99	Same as Ref. [21] Analysis by a pool of data from [18, 19, 27], N = 47	CrCl (↑) on CL (↑)
Nation et al., 2017 [17]	215 [a]	Critically ill including 29 receiving RRT	57.2	2.6	Same as Ref. [21]	CrCl (↑) on CL (↑)
Kristoffersson et al., 2020 [20]	349	Critically ill	69.5	4.1	CrCL, BW, IBW, SOFA score, infection site	CrCl (↑) on CL (↑)
Pediatric studies						
Ooi et al., 2019 [12]	5	Critically ill	7.1	1.6	BW, CrCl	BW (↑) on V (↑), CrCl (↑) on CL (↑)

APACHE II, The Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; BSA, body surface area; BT, body temperature; BUN, blood urea nitrogen; BW, body weight; CL, drug clearance; CrCl, creatinine clearance; CRRT, continuous renal replacement therapy; Hb, hemoglobin; Hct, hematocrit; HD, hemodialysis; IBW, ideal body weight; RRT, renal replacement therapy; SOFA, Sequential Organ Failure Assessment; V, volume of distribution. [a]105 patients from Garonzik et al, 2011 [21] with an additional 110 patients.

2.1.3.3. Pediatric pharmacokinetics

Nakwan et al. (2016) [15] conducted a study on 7 critically ill neonates with a median age of 13 days (range from 5 to 15 days). Colistin was given as a single dose of 5 mg of CBA/kg birth weight. Blood samples were collected before and at 15 min, 2, 4, 6, and 24 h after the end of colistin administration. Unfortunately, plasma colistin levels of all subjects at 6 h were less than 2 mg/L. The authors concluded that the current dose of colistin is suboptimal, higher dose, and different regimens should be studied. However, regarding a very specific and small number of subjects, the generalizability of this study is limited. Recently, Wacharachaisurapol et al. [25] conducted a study using NCA analysis on 20 pediatric patients and demonstrated that administering a loading dose of colistin improved drug exposure. A summary of PK parameters among these two studies is shown in Table 1.

2.1.4. Possible covariates on colistin pharmacokinetics

2.1.4.1. CrCl or eGFR

Colistin is primarily eliminated via non-renal pathways as described above in ADME summary. However, CMS, a prodrug of colistin, is predominantly cleared by the renal route but a fraction of the administered dose is hydrolyzed by plasma esterases to colistin. In patients with impaired kidney function, the CMS clearance would be decreased and a greater fraction of the administered dose of CMS would be converted to colistin [9]. Many adult PPK studies and one pediatric PPK study also observed the effect of CrCl on colistin CL (Table 2). The colistin dose recommendation regarding CrCl in adults is as shown in Table 3. Interestingly, adult patients with CrCl ≥90 mL/min would require a CMS dose of >5 mg of CBA/kg/day (calculating from the body weight of 60 kg). It is reasonable to explore the effect of CrCl or eGFR on colistin PK in pediatric patients. It also should be noted that the eGFR of pediatric patients is mostly calculated by using the modified (“bedside”) Schwartz equation: 0.413 × (height/SCr). Even though it is the most widely used one, there are some limitations for estimating GFR by using it because it is derived from chronic kidney disease (CKD) patients with a median age of 10.8 years (IQR, 7.7–14.3). Validation of using this equation outside the study population is lacking [28].

Table 3. Daily doses of colistin methanesulfonate (CMS) in adults for a desired target colistin $C_{ss,avg}$ of 2 mg/L for narrow windows of creatinine clearance. (modified from reference [17])

Creatinine clearance (mL/min)	CMS daily dose (mg of colistin base activity)	CMS daily dose/kg [a] (mg of colistin base activity)
0	130	2.2
5 to <10	145	2.4
10 to <20	160	2.7
20 to <30	175	2.9
30 to <40	195	3.3
40 to <50	220	3.7
50 to <60	245	4.1
60 to <70	275	4.6
70 to <80	300	5.0
80 to <90	340	5.7
≥90	360	6.0

[a] calculated from the body weight of 60 kg

2.1.4.2. Kidney biomarkers

Serum creatinine is the biomarker used for estimating CrCL or eGFR in both adults and children [28, 29]. Blood urea nitrogen (BUN) is the other biomarker associating with kidney function even though BUN might be more sensitive to some conditions, e.g., hydration status of patients, low or high protein intake, gastrointestinal bleeding, receiving cortisol [30]. Mohamed et al., 2012 [19] explored SCr as a plausible covariate in an adult PPK study and found no effect of SCr on colistin PK parameters. However, only one out of 10 patients in this study had an abnormal SCr. Grégoire et al. 2014 [26] explored both BUN and SCr effect on colistin PK parameters. It was found that the increase of BUN inversely associated with the decrease of colistin CL in this study.

2.1.4.3. Serum albumin

Plasma protein binding affects drug distribution in the body. Serum albumin is the major protein in plasma [31]. Colistin is bound to albumin up to 50% [11, 12]. Hypoalbuminemia which can be seen in patients with severe infections potentially affects the unbound plasma colistin concentration.

2.1.4.4. Body weight

Body weight is considered as a significant covariate for the PK parameters [31]. Ooi et al. [12] found that body weight was related to the volume of distribution of both CMS and formed colistin in a pediatric PPK study. There was extensive inter-individual variability in body weight regarding a wide age range of the patients. The effect of body weight could not be observed from adult studies (Table 2).

2.1.4.5. Age

Age may involve many demographics influencing the PK parameters rather than body weight [31]. Age-related changes to drug distribution are related to changes in body composition, the quantity of plasma proteins capable of drug binding, the quantity of hydrolysis enzymes such as esterases. In infants, a high percentage of body fluid is observed. Even though colistin is less water-soluble, CMS which is a prodrug of colistin is more water-soluble and might be affected by high body fluid composition [32, 33]. Esterase enzymes are the major hydrolysis enzymes of CMS. In neonates, the quantity of these enzymes is reduced [15]. This might cause a slow and low level of colistin compared with older children. Different SCr levels regarding the age groups are also observed as shown in Table 4 [34].

Table 4. Reference values of serum creatinine in children.
(modified from reference [34])

Age (year)	Serum creatinine values (mg/dL)
0-4	0.03-0.50
4-7	0.03-0.59
7-10	0.22-0.59
10-14	0.31-0.88
>14	0.50-1.06

Note: serum creatinine measured by the enzymatic method.

2.1.4.6. Gender

Gender affects the volume of distribution especially when the patients enter the adolescent period regarding the change of body composition [35]. Females are more likely to have a higher fat composition. Even though the relationship of this plausible covariate could not be demonstrated in adult studies, it is reasonable to investigate the effect of gender on PK parameters in pediatric patients.

2.1.5. Pharmacodynamics

2.1.5.1. PK-PD index of colistin

From *in vitro* studies, colistin is potent, concentration-dependent killing against MDR-GNB such as *P, aeruginosa,* and *A. baumannii* with a modest post-antibiotic effect at high concentrations [9]. For many concentration-dependent antibiotics, a maximum concentration in plasma (C_{max})/minimum inhibitory concentration (MIC) ratio of ≥8–10 is adequate for the treatment of GNB. However, there is no recommended C_{max}/MIC ratio for colistin. Recently, a study in mouse thigh and lung infection models demonstrated that the ratio of the area under the curve of the unbound colistin concentration in plasma (*f*AUC) across 24 h to MIC (*f*AUC/MIC) is the PK/PD index that correlates with the bacterial killing property [11]. $C_{ss,avg}$ of 2 mg/L has been proposed as an initial target concentration to meet the desired *f*AUC/MIC when treating bloodstream infection caused by MDR-GNB with the MIC of ≤2 mg/L [36]. However, the target $C_{ss,avg}$ of 2 mg/L might not be adequate for the treatment of pneumonia caused by MDR-GNB with the MIC of >1 mg/L regarding the poor distribution of colistin into the lung [11, 13].

2.1.5.2. Colistin MIC

Colistin MIC is measured by several methods, e.g., E-test, broth microdilution. The E-test method is no longer recommended regarding this method can produce very major errors (false susceptibility results) of up to 12% for Enterobacteriaceae and 33% for *P. aeruginosa* and *A. baumannii* [37, 38]. The reference method recommended by CLSI is broth microdilution [39], even though most of the microbiology laboratory could not routinely perform it regarding the method

difficulty. When evaluating the PK-PD index of colistin with a MIC value, it should be warranted about the method of MIC determination.

2.1.6. Clinical uses [40]

2.1.6.1. Approved indication

Colistin in form of CMS is approved for both adults and children for the treatment of acute or chronic infections caused by the following susceptible GNB: P. *aeruginosa*, *Enterobacter aerogenes*, *E. coli*, and *K. pneumoniae*. However, practically, colistin is also used for the treatment of *A. baumannii* infection regarding this pathogen is resistant to almost all of the available antibiotics including carbapenems except colistin.

2.1.6.2. Dose recommendation

The US FDA and European Medicines Agency (EMA) dose recommendation of intravenous or intramuscular injection for both adults and pediatric patients is CMS 2.5–5 mg of CBA/kg/day in 2–4 divided doses for patients with normal renal function. Colistin dose should be decreased regarding impaired kidney function. Recently, Nation et al. [17] suggested a colistin dosing scheme for adult patients with various kidney functions. Administering a loading dose of 300 mg of CBA is recommended followed by a maintenance dose regarding different creatinine clearances. No available recommendations for using colistin loading dose in pediatrics. In obese patients, dosage should be based on ideal body weight [40, 41].

2.1.7. Adverse drug reactions

2.1.7.1. Nephrotoxicity

Nephrotoxicity is the most common adverse drug reaction (ADR) of colistin. There is a variety of occurred nephrotoxicity, e.g., cylindruria, hematuria, proteinuria, elevated BUN or SCr [42]. However, reported nephrotoxicity in the literature is mostly based on the SCr–guided criteria including the elevation of SCr and the decline of creatinine clearance or eGFR which are calculated based on using SCr [5, 25, 43-48]. Acute kidney injury (AKI) is the nephrotoxicity defined by the Kidney Disease: Improving Global Outcomes (KDIGO) [49] which is a widely used definition.

In adults, the AKI rate was reported as 51% in patients using colistin while the matched control AKI rate was 22% [50]. AKI usually occurs when colistin is concomitantly given with other nephrotoxic drugs, e.g., vancomycin, aminoglycosides [51]. The steady-state trough colistin concentration of >2.42 mg/L showed association with nephrotoxicity in an adult study [52].

In children, colistin use causes less nephrotoxicity compared with adults. The nephrotoxicity rates reported among pediatric studies evaluating colistin efficacy and safety were ranged from 0 to 22.8% [5, 43-48, 53]. Among pediatric studies, the different nephrotoxicity rates may cause by many factors, e.g., patient characteristics, number of patients in the studies, nephrotoxicity definition, colistin dosing. Comparison of characteristics and reported nephrotoxicity among studies of pediatric patients receiving intravenous colistin is shown in Table 5.

2.1.7.2. Neurotoxicity

Neurotoxicity is the second most important ADR including dizziness, weakness, facial and peripheral paresthesia, vertigo, confusion, ataxia, and neuromuscular blockade. This ADR is less observed with CMS formulation [2]. No neurotoxicity was reported among pediatric studies [5, 25, 42, 44, 51, 54]. However, all study patients were critically ill or received sedative drugs while using mechanical ventilators, which potentially masked the neurotoxicity [45].

Table 5. Comparison of characteristics and reported nephrotoxicity rate among studies of critically ill pediatric patients receiving intravenous colistin.

Study	N	Age [a] (year)	Colistin dose [a] (mg of CBA/kg/day)	Duration of colistin [a] (day)	Nephrotoxicity (% (no. of case))	Nephrotoxicity definition
Nephrotoxicity defined by using the increase of SCr >1.5–2 times of the baseline						
Falagas et al., 2009 [43]	7	11 (1.2–13)	Fixed dose, 2.1	10 (min–max, 2–23)	0	SCr >1.5 times or >1.3 mg/dL
Karbuz et al., 2014 [46]	29 (38 courses)	1.4 (0.3–18)	2.5 (1.7–2.7) or 5.0 (2.3–5.6)	12 (2–37)	2.6 (1/38)	SCr >2 times or SCr > normal value
Ozsurekci et al., 2016 [55]	64 (73 courses)	2.5 (0.7–10.5)	N/A	17.0 (12.0–30.0)	4.1 (3/73)	SCr >2 times
Sahbudak Bal et al., 2018 [47]	94 (104 courses)	Median, 4.7	5.0 [b]	12.5 ± 6.4	10.5 (11/104)	SCr >1.5 times
Nephrotoxicity defined by using the decrease of Cl_{Cr} or the increase of SCr						
Karli et al., 2013 [45]	31 (41 courses)	3 (min–max, 0.3–17.0)	4.9 ± 0.5 [b]	19.8 ± 10.3	7.3 (3/41)	Decreased CrCl >50% or SCr >1.1 mg/dL
Kapoor et al., 2013 [5]	50	3.0 (0.1–12)	1.7–2.5	Mean, 14.3 (range, 7–21)	10.0 (5/50)	Decreased CrCl >30% or SCr >2 times
Paksu et al., 2012 [44]	79 (87 courses)	2.5 (0.3–18.0)	2.25 ± 0.25	17.2 ± 8.4	2.3 (2/87)	Decreased CrCl >50% or SCr >1.1 mg/dL
Tamma et al., 2013 [48]	92	16 (11–17.5)	5 [b] (non-cystic fibrosis) or 7.5 (cystic fibrosis)	N/A	22.8 (21/92)	CrCl ≤60mL/min, or decrease in the category of clearance

ARC, augmented renal clearance (eGFR >150 mL/min/1.73 m^2) ; CBA, colistin base activity; CrCl, creatinine clearance; N/A, not available; SCr, serum creatinine.

[a] Data are shown in mean ± standard deviation or median (range) or described otherwise.

[b] No available data whether it was mg of CBA or colistin methanesulfonate.

[c] Nephrotoxicity rate within the first week after intravenous colistin initiation.

2.1.8. Colistin determination

2.1.8.1. Colistin and CMS stability

CMS in plasma is hydrolyzed by esterases into formed colistin. At 37 °C, CMS in plasma is hydrolyzed to formed colistin less than 10% after 2 h. However, CMS is hydrolyzed up to 30%, 50%, and 65% at 6, 12, and 24 h, respectively [56]. Blood samples should be processed and stored as soon as possible or within 2 h to avoid further conversion of CMS into formed colistin after collection. Besides the time issue, the sample processing method also affects colistin concentration in sample. Strong acid and excessive heat during the sample preparation process cause further conversion of CMS into formed colistin and lead to colistin overestimation [56, 57]. Reed et al. [58] reported an extraordinarily high plasma colistin C_{max} of 21.4-23 mg/L in cystic fibrosis patients compared with 2.4–5.4 mg/L reported for other studies (Table 1). From Reed et al. study, plasma samples were treated with perchloric acid and hydrochloric acid and heated at 54 °C for 1 hour. Pretreatment at 54°C with acids may accelerate the hydrolysis of CMS to formed colistin and would potentially be the result of high C_{max}.

2.1.8.2. Methods of colistin determination

Colistin determination can be separated into 2 steps including the separation process and the detection process. The separation process can be performed by liquid chromatography (LC) technic. Separation of the individual components of a mixture occurs when the mixture travels into a non-polar stationary phase (column) by a polar mobile phase. In the past, this process occurred by using gravity for sample traveling in the machine. Currently, a high-pressure pump is applied to the system to accelerate processing time. So, this technic is called high performance (also known as high pressure) liquid chromatography (HPLC). For the detection process, it could be done by several technics, e.g., ultraviolet (UV) absorbance detecter, fluorescent detecter, depending on the chemical property of the substance. Many substances including colistin need to be derivatized for better detection [59, 60]. The disadvantage is that sample needs more processes before determination. A more recent technic is liquid chromatography with tandem mass spectrometry (LC-MS/MS). LC-MS/MS is a hybrid system in which a mass spectrometer replaces the more usual UV absorbance detector

in an HPLC system. Mass spectrometry ionizes atoms or molecules to facilitate their separation and detection in accordance with their molecular masses and charges (mass to charge ratio). MS method of detection results in a lower limit of detection regarding more sensitivity.

HPLC methods for colistin determination were reported during 2001-2011 [21, 58, 60]. Some showed limitations as mentioned above such as in Reed et al. study. All of the HPLC methods reported also have a limitation on sample derivatization before colistin determination. Recently, LC-MS/MS is a preferred method for colistin determination in both adult and pediatric colistin pharmacokinetic studies [12, 17, 19, 20, 25, 27].

2.2. Population pharmacokinetics by using nonlinear mixed-effects models approach

2.2.1. Background

The PK study is the study considering the drug movement through the body. This involves the absorption, distribution, metabolism, and elimination of drugs and their metabolites. It is crucial to understand what the human body interacts with any drugs especially for the dosing recommendation including dosage, route of administration, and intervals. The traditional PK study is relatively simple and straightforward, however, there are some limitations and disadvantages. The PPK approach is the current standard tool for estimating the PK parameters and appropriate dosing at one step by using computerized modeling. The advantages and disadvantages of both methods are shown in Table 6 [61, 62].

In detail, PPK is the study to obtain relevant pharmacokinetic information in patients who are representative of the target population. Certain patient demographics (e.g., body weight, age, sex, pharmacogenomics), pathophysiology, and the presence of other therapies can regularly alter dose-concentration relationships. Sources of variability, such as intersubject, intrasubject, and inter-occasion are obtained and quantified by this study during drug evaluation. PPK also seeks to quantitatively estimate the magnitude of the unexplained part of the variability in the patient population [61].

Table 6. Comparison of traditional and population pharmacokinetics.

	Traditional approach	**Population PK approach**
Number of subjects	Typically, 8–16	Usually more than 40
Type of subjects	Usually performed in healthy subjects	Target population
Number of samples	Intensive (typically more than 10)	Sparse
Sampling schedule	Fixed	Varied
Evaluation for PK parameters	Simple calculation	Time-consuming and requiring skilled pharmacokineticists/pharmacometricians
Covariate identification	Difficult	Yes, quantified

The nonlinear mixed-effects (NLME) model approach currently is the standard method for population pharmacokinetics. This approach incorporates both fixed effects and random effects in the model and allows them to be expressed as a nonlinear function [63]. The number of samples per subject used for this approach is typically small, ranging from one to six. As does the pooled analysis technic, the NLME approach analyzes the data of all individuals at once but takes the interindividual random effects structure into account. This ensures that confounding correlations and imbalance that may occur in observational data are appropriately accounted for [64].

2.2.2. Model development [65]

Model development is initiated by identifying a base model composed of a structural model and variance models. The structural model is the model that best describes the data without covariates, such as one- or two-compartment model. A plot of concentration-time profile for population data set would help reveal patterns and structure in the data and would lead to selecting the most appropriate and simplest one. The variance models consist of two main sources of variability including interindividual variability (IIV) and residual variability (RV). IIV is the variance of a parameter across

different individuals in the population; RV is the unexplained variability in the observed data after controlling for other sources of variability. IIV should be assumed as a lognormal distribution regarding its biological variation by nature is lognormal. The base model which consists of the simplest structural, IIV, and RV models will be chosen by considering the objective function value (OFV), which is comparable to twice negative log-likelihood (-2LL), Akaike information criterion (AIC), Bayesian information criterion (BIC), and graphical examinations.

Afterward, covariate model building is performed. Covariates selected should have a physiological rationale for their inclusion in the base model or be described previously in the literature. Then the stepwise forward addition and backward elimination are implemented to obtain the final model. Based on the χ^2 test, the covariate is considered as a significant one in the forward addition step when it reduces -2LL significantly (e.g., a reduction of -2LL >6.64 correspondings with $P < 0.01$, degree of freedom = 1). Then, a backward elimination step is performed. The covariate will be retained in the final model when it causes an increase of -2LL significantly (e.g., a reduction of -2LL >10.83 correspondings with $P < 0.001$, degree of freedom = 1) when it is sequentially removed from the full model during backward elimination.

2.2.3. Model evaluation

2.2.3.1. Goodness-of-fit plots [66]

Goodness-of-fit plots are graphically assessed for the accuracy of a model. Goodness-of-fit assessments require diagnostic plots, such as the observed concentrations (DV) versus individual-predicted concentrations (IPRED) or population-predicted concentrations (PRED); the conditional weighted residuals (CWRES) versus population-predicted concentrations (PRED) or time after dose (TAD). If the model could well describe the data, the line of identity (intercept 0 and slope 1) should run through the center of DV versus IPRED and PRED plots. The plots of CWRES should be scattered evenly above and below the zero reference line (intercept 0 and slope 0) and within +2, -2.

2.2.3.2. Bootstrap [66]

The bootstrap method is performed to assess the reliability of the final model. Practically, 1,000 data sets will be generated by random sampling with replacement from the original data. The final model parameters will be all estimated, and their median and 95% CI will be also calculated. Bootstrap is considered successful if the 95% CI for each parameter encompassed the initial estimate parameter and met the prespecified convergence rate (95% CI does not include zero).

2.2.3.3. Visual predictive check [67]

A visual predictive check is used to assess predictive performance. The estimated parameters of the model are fixed and used for simulating a certain number of a virtual data set, e.g., 1,000 replicates. Then, observed data are compared to the simulated data. If the model has adequate predictive performance, the observed data will lie within the 90% CI of the corresponding quantiles of simulated data. However, when the difference of predictions within a bin is mainly due to different values of other independent variables, e.g., dose, covariates, the diagnosis may be problematic or misleading. Prediction-corrected VPC (pcVPC) differs from traditional VPC in that the dependent variable has been subject to prediction correction before the statistics are calculated. The variability coming from variations in independent variables within a single bin is removed by normalizing the observed and simulated dependent variable based on the typical population prediction. pcVPC is a more informative diagnostic tool for assessing mixed-effects models that facilitates the development of more predictive models and hence result in better possibilities for model-based decision making.

2.3. Monte Carlo simulation for pharmacodynamic assessment

Monte Carlo simulation or simulation is a method that incorporates the interindividual variability in PK among potential patients to model the probability of different outcomes. First, the PPK model consists of all those elements that link the known inputs into the system (e.g., dose, dosing regimen, PK model, PK/PD model, covariate-PK/PD relationships, disease progression) to the outputs of the system (e.g., exposure, PD response, outcome, or survival) is created. Then, the simulation will be done. The outputs of the system are driven by the inputs into the system and may reflect

something as simple as exposure (area under the curve, PK parameters, or C_{max}) or something more complicated, such as survival. The number of replications that is sufficient to observe rare events is in the thousands regarding rare events rarely occur and large numbers are needed to see them. Large replicate numbers are also needed to obtain confidence intervals or estimates of variance components [68, 69].

CHAPTER III METHODOLOGY

Prior to this study, a prospective, traditional full pharmacokinetic study of intravenous colistin in 20 pediatric patients with an age range of 2.2–14.9 years was conducted regarding the lack of PK data in the pediatric population (study 1, the clinical trial registry number: TCTR20171119001, http://www.clinicaltrials.in.th). The main objectives of the study were to understand the PK characteristics of intravenous colistin and to explore the PK benefit of administering an intravenous colistin loading dose. In this study, a prospective, multicenter, population pharmacokinetic study was conducted to gain more understanding about PK characteristics in the pediatric population (study 2). The age ranges of study participants were also broadened into infants from 1 month of age for better generalizability of the data in the population. With larger study participants, the effect of plausible covariates on colistin PK parameters could be tested and quantified. The dose recommendation could also be generated. Apart from the PK study, a retrospective study in larger pediatric patients was conducted for more understanding of the association of colistin, especially when giving a loading dose, and the rate of AKI in this population (study 3). The scope and characteristics of each study are summarized in Table 7. The methodology of the population pharmacokinetic study (study 2) is described in this chapter. The methodology of study 3 is described in Appendix A.

Table 7. Scope and characteristics of three studies on intravenous colistin in pediatric patients.

	Study 1	Study 2	Study 3
Study design	Prospective, traditional, full PK study	Prospective, multicenter, population PK study	Retrospective study
Inclusion criteria for age	2–18 years	1 month–12 years	1 month–18 years
Enrollment period	Aug 2014– Apr 2018	KCMH Mar 2018–March 2021 QSNICH Oct 2018–Dec 2020	KCMH 2014–2019
Number of patients	20 (KCMH) (7-8 blood samples/subject; sampling time: 1, 2, 4, 8, 12 (only for patients who were prescribed colistin every12 h), 24, 48, and 72 h after the first dose)	59: KCMH 19; QSNICH 40 For population PK analysis, 79 were enrolled (59 from study 2 and 20 from study 1)	181 (including 20 from study 1 and 15 of KCMH from study 2)
Age, median (interquartile range)	8.5 years (3.5–11.3)	2.6 years (0.8–6.8)	2.0 years (0.7–6.9)
Age range (min–max)	2.2–14.9 years	1 month–14.9 years (pooled participants of study 1 and 2)	1 month–17.1 years

KCMH, King Chulalongkorn Memorial Hospital; PK, pharmacokinetic; QSNICH, Queen Sirikit National Institute of Child Health.

3.1. Study design

This study is a prospective, multicenter, population pharmacokinetic study of intravenous colistin in pediatric patients. The clinical trial registry number is TCTR20180526001 (http://www.clinicaltrials.in.th).

3.2. Patients and methods

3.2.1. Population and samples

3.2.1.1. Target population: pediatric patients

3.2.1.2. Study population: pediatric patients who were hospitalized at King Chulalongkorn Memorial Hospital (KCMH), Faculty of Medicine, Chulalongkorn University or Queen Sirikit National Institute of Child Health (QSNICH), Department of Medical Services, Ministry of Public Health.

3.2.1.3. Sample size calculation

The general recommendations for the sample size of not less than 40 [62] and the number of blood samples of 1–6 per subject in various times [70] for the population pharmacokinetic study were applied. The number of participants in this study was 60 with 2–6 blood samples per participant.

3.2.1.4. Study participants: 60 patients

- Thirty-five patients with the age of 1 month to 2 years
- Twenty-five patients with the age of > 2 years to 12 years

3.2.1.5. Inclusion criteria

- Patients aged from 1 month to 12 years at the day of the first dose of colistin given
- Adequate vascular access to enable blood collection
- Written informed consent by a caregiver

3.2.1.6. Exclusion criteria

- Body weight < 3 kg

- Receiving intravenous colistin > 5 doses at the day of enrollment
- Receiving renal replacement therapy (RRT) or extracorporeal membrane oxygenation (ECMO)
- Received any routes of colistin within 14 days prior to the day of enrollment
- Concomitantly receiving another route of colistin rather than an intravenous injection

3.2.2. Data collection

The following data were recorded in the case report form:

- Demographic data: age, sex, actual body weight, height or length, underlying disease
- Laboratory data: SCr, eGFR (0.413 × height/SCr [28]), Alb, complete blood count
- Microbiological data
- Indication for colistin use
- Colistin dosage regimen: mg of CBA per kg/dose, actual administration time, infusion time, dosing interval

3.2.3. Recommended dose of colistin

- The formulation of colistin injection was CMS including Mellistin™ injection (equivalent to 150 mg of CBA/vial), Siam Pharmaceutical Co. Ltd., Bangkok, Thailand (KCMH) (Appendix B), and Colistin-150™ injection (equivalent to 150 mg of CBA/vial), Universal Medical Industry Co. Ltd., Bangkok, Thailand (QSNICH) (Appendix C).
- Loading dose: 4 mg of CBA/kg/dose
- Maintenance dose: 5 mg of CBA/kg/day divided into every 8–12 h intervals
- Each dose of colistin should be dissolved in 5–10 mL of normal saline solution and infused intravenously via infusion pump over 30 min.

- The first maintenance dose should be started 12 h after administering a loading dose.
- Colistin could be prescribed otherwise regarding the attending physician's judgment.

3.2.4. Blood sampling

- 3 mL of whole blood in EDTA tube per sample
- 60 patients were stratified by age into 2 groups (Figure 3): group A was 1 month to 2 years of age (35 subjects); group B was > 2 years to 12 years of age (25 subjects).
  - Group A
    - At least 20 patients: 2–3 blood samples were collected after the 1st dose of colistin.
    - The rest: 2–3 blood samples were collected after the 6th dose of colistin.
  - Group B
    - At least 10 patients: 3 blood samples were collected after the 1st dose and the 6th dose of colistin.
    - The rest: 3 blood samples were collected after the 1st dose or the 6th dose of colistin.
- Blood sampling times were varied regarding drug intervals (Table 8).
- The actual time of colistin administration and blood sampling were recorded.

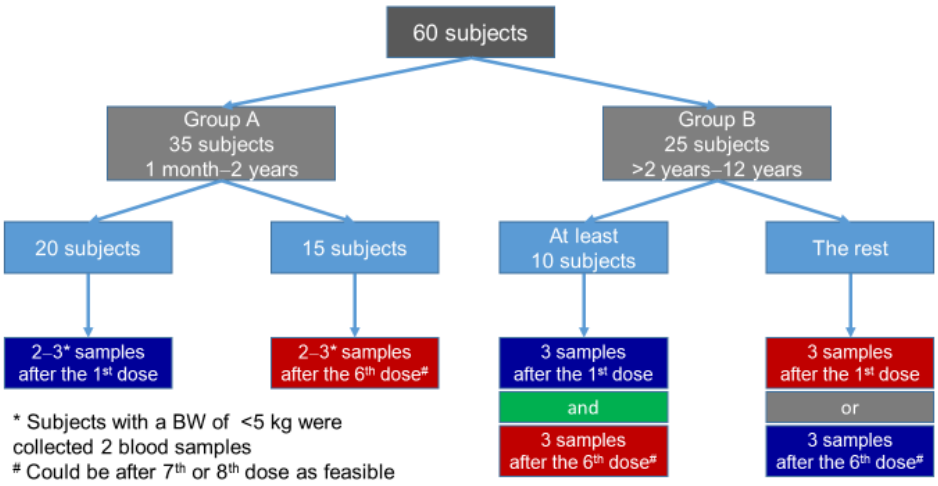


Figure 3. Blood sampling stratification.

Table 8. Blood sampling schedule varied by colistin administration intervals.

Interval (h)	Time (h) after starting colistin infusion [a] 0.5–1	2–4	6–8	6–12	12–24
8	X	X	X		
12	X	X		X	
24		X	X		X

[a]Any two out of three sampling times could be selected for the patients who need to be collected only 2 blood samples.

3.2.5. Determination of colistin concentration in plasma

- Blood samples were transported from clinical sites to the Chula Clinical Research Laboratory (CRL) under 4 °C and were processed within 2 h after collection.
- Blood samples were centrifuged at 4000 RPM under 4 °C. Plasma samples were stored at -70 °C until analysis.
- Plasma formed colistin (colistin A + colistin B) was determined at the Clinical Pharmacokinetics and Pharmacogenomics Research Unit, Department of Pharmacology, Faculty of Medicine, Chulalongkorn

University, Bangkok, Thailand by using liquid chromatography-tandem mass spectrometry (LC-MS/MS) method (Shimadzu LCMS-8040 triple quadrupole mass spectrometer by Shimadzu Corporation, Kyoto, Japan) as previous reports with modifications [71, 72]. A volume of 200 µL of plasma was mixed with 10 µL of internal standard solution (40 mg/L of netilmicin sulfate) and 200 µL of distilled water. The mixture was loaded onto solid-phase extraction (SPE) column (Oasis® HLB SPE cartridges) preconditioned with 1 mL of methanol followed by 2 mL of distilled water. The SPE column was flushed with 1 mL of 5% methanol. The analytes were then eluted with 1.4 mL of 0.1% formic acid in methanol (vol/vol). The eluate was evaporated at 30 °C and the residue was reconstituted with 400 µL of the mobile phase, and 10 µL of the reconstituted sample was injected into the LC-MS/MS system. The separation process was run through the XBridge HILIC 3.5 µm 3×150 mm column at a flow rate of 200 µL/min. The mobile phases were 0.1% formic acid in acetonitrile (vol/vol) and 0.1% formic acid in distilled water (vol/vol). Electrospray ionization in the positive-ion mode and multiple reaction-monitoring were used. The mass-to-charge ratios (m/z) were 585.5/101.1 for colistin A, 578.5/101.1 for colistin B, and 476.25/191.25 for netilmicin sulfate (the internal standard). The validated assay ranges of formed colistin were 0.1-6.4 mg/L (see Appendix C for LC-MS/MS method validation). The plasma samples which exceeded colistin from the validated ranges were further diluted and repeated determination.

3.2.6. Population pharmacokinetic analysis and simulation

3.2.6.1. Software

PPK analysis and simulation were performed using Phoenix™ version 8.3. A nonlinear mixed-effects model was developed using the first-order conditional estimation-extended least-squares (FOCE ELS) method. Plasma colistin concentration data from the current study and study 1 [25] were simultaneously analyzed.

3.2.6.2. Model development

- Structural model: One- and two-compartment models were explored by observing the log-concentration versus time profiles of 20 sample-rich participants, and goodness-of-fit plots.
- Variance models: For the colistin population pharmacokinetics model, the IIV was described by the exponential error model [12, 73]. To find out the residual variability of the parameters, the additive, proportional (so-called multiplicative in Phoenix software), and additive with proportional residual error models were tested.
- Covariate model: The potential covariates were considered including age, sex, SCr, eGFR (so-called CrCl), and serum albumin. Covariates were screened with a stepwise approach. During the forward addition step, covariates were added to the model. The significant covariates in this step were defined by a reduction of -2LL >6.64 ($P < 0.01$). All covariates that met these criteria were included in the full model. Then, a backward elimination step was done in which each covariate was sequentially removed from the full model. The covariates were retained in the final model when there was an increase of -2LL >10.83 ($P < 0.001$) during backward elimination step.
- Covariance model: Diagonal and non-diagonal models were tested. Model selection was based on statistical significance between models using -2LL, AIC, and BIC.

3.2.6.3. Final model evaluation

- Goodness-of-fit plots were performed to qualify the final model, which included PRED and IPRED versus DV, and CWRES versus PRED and TAD.
- Bootstrap was performed for evaluating the stability and robustness of the final model. Repeated random sampling with replacement from the original data set generated 1000 replicates. Median values of

estimated parameters with 95% CI from the bootstrap method were compared with those estimated from the original dataset.

- The prediction-corrected visual predictive check was used for internal model validation. One thousand times simulation replicates of the original data set were performed with the final model. The 5^{th}, 50^{th}, and 95^{th} percentiles with the 90% CI of them were calculated. Then, the observed concentrations were plotted against TAD and the observed concentrations were compared with the distribution of simulated data.

3.2.7. Pharmacodynamic assessment using simulation

Regarding the parameter estimates from the final PPK model, a set of CL (10,000 replicates in each clinical scenario) was simulated. The IIV and RSV were included in this simulation. The dosing schemes were set at 5, 7.5, 10, and 12.5 mg of CBA/kg/day divided into 12-h intervals. Each colistin dose was set as a 30-min intravenous infusion. The $C_{ss,avg}$ was calculated using simulated CL as follows,

$C_{ss,avg}$ (mg/L) = AUC_{24h} (mg/L*h)/24 (h), when AUC_{24h} = dose per day (mg/kg)/CL (L/kg*h)

The probability of target attainment (%PTA) was predicted across the target $C_{ss,avg}$ of 0.25, 0.5, 1.0, 2.0, and 4.0 mg/L.

3.2.8. Statistical analysis

3.2.8.1. Baseline characteristics and microbiological data were reported as median with interquartile range (IQR) for continuous variables, and count with percentage for categorical variables.

3.2.8.2. Study 2: Population pharmacokinetic analysis and simulation were performed. The detail for analysis is described in section 3.2.6. Population pharmacokinetic analysis and simulation.

3.2.8.3. Study 3: Factors associated with AKI were assessed using univariable and multivariable logistic regression and are presented using odds ratios and 95% CI with P–values of Z–test. Factors with the association of $P < 0.1$ in

univariable analysis were selected for further multivariable analysis. The interested different initial doses of colistin treatment were included in the multivariable model for adjusting the association with AKI. Stata/SE version 13.0 was used for all data analyses.

3.3. Study outcomes

3.3.1. The primary outcome: the estimated parameters (V, CL) of the formed colistin and the covariate(s) influencing the PK parameters

3.3.2. The Secondary outcomes

- The dose recommendation of intravenous colistin regarding significant covariates
- The associated factors of AKI rates in pediatric patients administered with intravenous colistin.

3.4. Ethical considerations

The study protocol was submitted to the Institutional Review Board of both clinical research sites (KCMH and QSNICH) and approved before patient enrollment (Appendix D). Ethical considerations were as follows:

- Respect of person: The investigators described the study procedure and provided clear and adequate information before receiving consent. Written informed consent was obtained from the parents of all participants. Written informed assent was obtained from the participants aged ≥7 years, if appropriate. The participants could independently decide whether to join the study or not without any effects on their medical management. Participants were able to withdraw from the study at any time. The investigators will keep the patient's information confidential.
- Beneficence: Participants would not receive any direct benefit from this study but the valuable data from this study will guide the clinicians to be able to choose the appropriate dose of colistin for the other patients in the future.
- Justice: Patients who met the inclusion criteria without any exclusion criteria were equally eligible to participate in this study.

CHAPTER IV RESULTS

4.1. Demographic and clinical data

4.1.1. Patient demographics

From March 2018 to February 2021, 59 patients were enrolled (19 from KCMH, 40 from QSNICH). The proposed sample size described in the methodology was 60, however, the COVID-19 situation in Thailand and also in Bangkok is getting worse resulting in the obstacle of patient enrollment. The enrollment process was stopped at 59 patients. This would not affect the PPK analysis process. Of 59 patients, 34 were in group A (age 1 month to 2 years), 25 were in group B (age > 2 years to 12 years). Together with 20 patients from KCMH from the previous study, a total of 79 patients were eligible for this study. Of these patients, 39 (49.4%) were male, and the median age was 2.6 years (IQR, 0.8–6.8 years); 61 (77.2%) had at least one comorbidity which malignancy was the most common; 73 (92.4%) were admitted to intensive care units (ICU). The most common colistin indication was ventilator-associated pneumonia. Patient demographics are summarized in Table 9. Median baseline serum creatinine classified by age groups are summarized in Table 10 and demonstrated that younger infants and children had lower baseline SCr compared with older children.

4.1.2. Colistin administration

A colistin loading dose of 4–5 mg of CBA/kg/dose was administered in 38 (48.1%) patients: 29 (74.4%) of KCMH patients; 9 (22.5%) of QSNICH patients. The 12-h dosing interval was the majority (*n* = 69 (87.3%): 29 (74.4%) of KCMH patients; 40 (100%) of QSNICH patients. Median colistin maintenance dose was 5.0 mg of CBA/kg/day (IQR, 4.9–5.0).

4.1.3. Microbiological data

Bacterial cultures were obtained from 79 patients including tracheal suction culture (*n* = 54, 68.4%), hemoculture (*n* = 20, 25.3%), urine culture (*n* = 4, 5.1%), and wound swab culture (*n* = 1, 1.3%). Of the 79 patients, 47 (59.5%) were positive for MDR-GNB of interest including: *A. baumannii* (*n* = 34; carbapenem-resistant isolates = 29, 85.3%), Enterobacteriaceae (*E. coli*, *K. pneumoniae*, and *Enterobacter* spp.) (*n* =

10, carbapenem-resistant isolates = 4, 40%), and *P. aeruginosa* (*n* = 3; carbapenem-resistant isolates = 2).

Table 9. Patient demographics.

Characteristics, N = 79	Results[a]
Age, year	2.6 (0.8–6.8)
Age group	
1–12 months	21 (26.6)
>1–2 years	13 (16.4)
>2–4 years	18 (22.8)
>4–7 years	8 (10.1)
>7–10 years	9 (11.4)
>10–15 years	10 (12.7)
Weight, kg	12.0 (7.4–20.0)
Height or length, cm	90.0 (68.0–113.0)
Baseline eGFR, mL/min/1.73 m^2	147.8 (102.5–186.9)
Baseline serum creatinine, mg/dL	0.25 (0.19–0.32)
0.10–0.20	27 (34.2)
0.21–0.30	32 (40.5)
0.31–0.40	9 (11.4)
0.41–0.50	5 (6.3)
0.51–0.75	6 (7.6)
Serum albumin, g/dL	3.3 (3.1–3.6)
Comorbidity	61 (77.2)
Malignancy	23 (29.1)
Neurologic disease	14 (17.7)
Chronic cardiac disease	10 (12.7)
Chronic pulmonary disease	9 (11.4)
Receiving immunosuppressive agent	7 (8.9)
Others	4 (5.1)

Intensive care unit admission	73 (92.4)
Receiving colistin loading dose[b]	38 (48.1)
Colistin maintenance dose, mg of CBA/kg/day	5.0 (4.9–5.0)
Colistin indication[c]	
Ventilator-associated pneumonia	53 (67.1)
Sepsis/CLABSI/CRBSI	24 (30.4)
Urinary tract infection	4 (5.1)
Skin and soft tissue/surgical site infection	3 (3.8)
Intraabdominal infection	1 (1.3)

CBA, colistin base activity; CLABSI, central line-associated bloodstream infection; CRBSI, catheter-related bloodstream infection; eGFR, estimated glomerular filtration rate.

[a] data are shown as count (%) or median (interquartile range).

[b] colistin methanesulfonate 4–5 mg of CBA/kg/dose.

[c] Some patients were diagnosed with >1 clinical syndromes.

Table 10. Median baseline serum creatinine classified by age groups.

Age groups	n (%)	Median SCr (IQR)
1–12 months	21 (26.6)	0.24 (0.20–0.29)
>1–2 years	13 (16.4)	0.20 (0.17–0.29)
>2–4 years	18 (22.8)	0.21 (0.18–0.27)
>4–7 years	8 (10.1)	0.20 (0.17–0.33)
>7–10 years	9 (11.4)	0.34 (0.27–0.57)
>10–15 years	10 (12.7)	0.42 (0.30–0.51)

IQR, interquartile range; SCr, serum creatinine.

4.1.4. The association of giving an intravenous colistin loading dose and rates of AKI

From study 3, A total of 181 children were enrolled. Ninety-five patients (52.5%) were male. The median age was 2.0 years (IQR, 0.7–6.9). All patients were prescribed colistin with concomitant antibiotics. Three most common concomitant antibiotics were meropenem (70.2%), sulbactam-containing antibiotics (ampicillin/sulbactam, cefoperazone/sulbactam, or sulbactam) (44.2%), and aminoglycosides (amikacin or gentamicin) (12.7%).

Data on SCr were available in all patients (n = 181) at the 1st week after colistin initiation, and 170 (93.9%), 87 (48.1%), and 39 (21.5%) at the 2nd, 3rd, and 4th week, respectively. Overall AKI rates within the 1st week and the 4th week after colistin initiation among patients without impaired kidney function at baseline (eGFR ≥80 mL/min/1.73 m^2) (n = 157) were 20.4% (32/157) and 29.3% (46/157), respectively. Augmented renal clearance (eGFR ≥150 mL/min/1.73 m^2) may cause falsely low SCr at the baseline, of which the definition of 1.5 times SCr may bias towards a high rate of AKI. Therefore, a subset of data that included only 94 patients with a baseline eGFR of 80–150 mL/min/1.73 m^2 was re-analyzed. Overall AKI rates within the 1st week and the 4th week after colistin initiation were 12.8% (12/94) and 21.3% (20/94), respectively. Stage 1 AKI still was the most common (n = 13, 65.0%). Administering a loading dose was not associated with AKI. The factor that was associated with AKI was concomitant nephrotoxic agents (Table 11). The overall 30-day mortality rate was 11%.

Table 11. Association of characteristics of pediatric patients without impaired kidney function at baseline administered with intravenous colistin and acute kidney injury.

	Total	With AKI *n* (%)	Crude OR (95% CI)	P-Value	Adjusted OR (95% CI)	P-Value
Total	157	46 (29.3)				
The first dose of colistin treatment						
Loading dose	62	16 (25.8)	1		1	
Standard dose	95	30 (31.6)	1.33 (0.65–2.71)	0.44	1.30 (0.61-2.77)	0.49
Colistin treatment duration in days						
1–7	79	23 (29.1)	1			
8–14	50	13 (26.0)	0.84 (0.38–1.86)	0.67		
15–30	28	10 (35.7)	1.33 (0.53–3.31)	0.54		
Age						
>2–18 years	82	19 (23.2)	1		1	
1 month–2 years	75	27 (36.0)	1.86 (0.93– 3.74)	0.08	1.83 (0.88-3.81)	0.10
Gender						
Female	77	21 (27.3)	1			
Male	80	25 (31.2)	1.21 (0.61–2.41)	0.58		
Co−morbidity						
No	16	3 (18.7)	1			
Yes	141	43 (30.5)	1.90 (0.52–7.02)	0.34		
Colistin indication						
Others [a]	19	3 (15.8)	1		1	
Sepsis/ CRBSI/ CLABSI	82	22 (26.8)	1.96 (0.52, 7.37)	0.32	1.87 (0.45-7.73)	0.39
VAP	56	21 (37.5)	3.2 (0.83, 12.30)	0.09	3.62 (0.85-15.41)	0.08
No. of concomitant nephrotoxic drugs being prescribed within 3 days after colistin initiation						
0	15	1 (6.7)	1		1	
1–2	116	33 (28.4)	5.57 (0.70–44.04)	0.10	5.25 (0.63-43.88)	0.13
≥3	26	12 (46.2)	12.00 (1.37–105.13)	0.02	13.99 (1.49-131.63)	0.02

AKI, acute kidney injury; CI, confidence interval; CLABSI, central line–associated bloodstream infection; CRBSI, catheter–related bloodstream infection; OR, odds ratio; VAP, ventilator–associated pneumonia.

[a] Others included urinary tract infection, surgical site infection, and intraabdominal infection.

4.2. Population pharmacokinetic analysis

Data were obtained from Study 1 (20 patients, 147 plasma samples) and Study 2 (59 patients, 187 plasma samples) to form a data set of 334 plasma colistin concentrations and used for population PK modeling. Plasma colistin concentration versus time profile is shown in Figure 4.

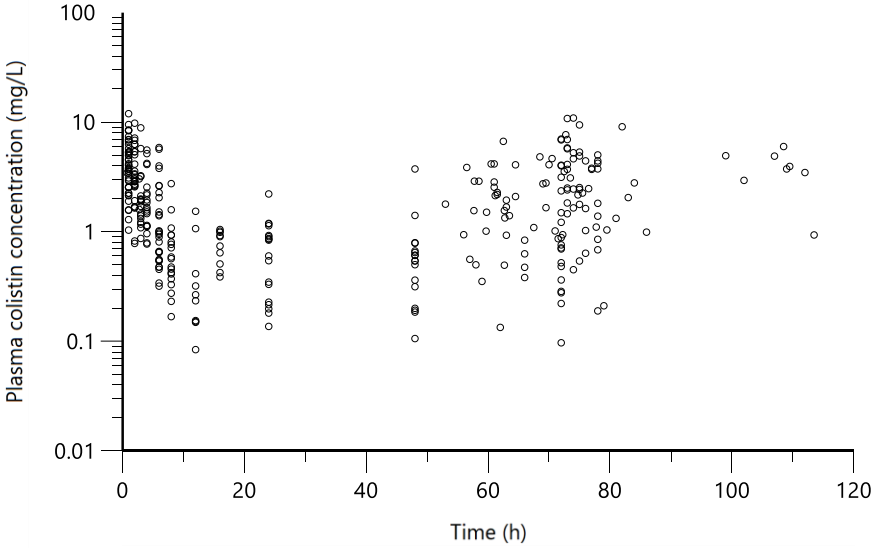


Figure 4. Plasma colistin concentrations versus time profile of pediatric patients after receiving intravenous colistin.

4.2.1. Base model

Plasma colistin concentration-time profiles and goodness-of-fit plots for the structural model from 20 sample-rich patients are shown in Figures 5 and 6, respectively. The PK characteristics of colistin were well described by the one-compartment model with first-order elimination. The population base model was parameterized in terms of the volume of distribution (V) and clearance (CL). The IIV was described by an exponential error model:

$$P_i = \theta(P) \times \exp(\eta_i)$$

where P_i is the PK parameter estimation of the i^{th} subject, $\theta(P)$ is the typical value, and η_i is a random variable for individual i^{th}, which is a normally distributed random variable with mean zero and variance ω^2.

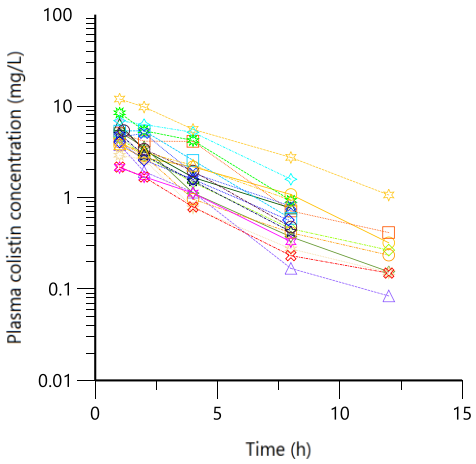


Figure 5. Plasma colistin concentrations versus time profile of 20 patients after administering the first dose of colistin.
(data from Study 1 [25]).

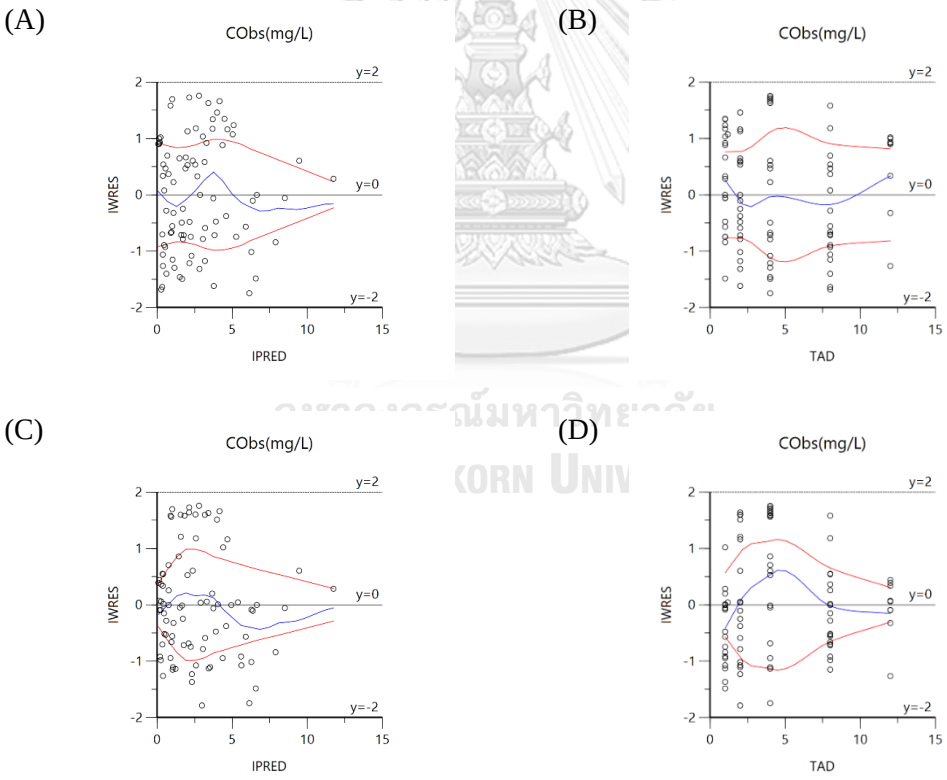


Figure 6. Goodness-of-fit plots for the structural model.
1-compartment (A, B) 2-compartment (C, D). Cobs, observed concentration; IPRED, individual-predicted concentrations; IWRES, individual weighted residuals; TAD, time after dose. The blue line is trend line, and the red line is trend line of absolute IWRES.

The residual variability (RV) models including additional, proportional, and additional with proportional were compared. The comparisons of -2LL, AIC, BIC, and population pharmacokinetic parameter estimates in this process are shown in Table 12. Even though the additional with proportional RV model resulted in the lowest -2LL (796.454), it was not significantly different from the result of the proportional RV model (796.726). Moreover, the proportional RV model resulted in lower values of AIC and BIC. The proportional RV model was selected. Therefore, the one-compartment model with exponential IIV and proportional RVmodel was the appropriate base model for the next step. Goodness-of-fit plots for the base model are shown in Figure 7 A, B and Figure 8 A, B. The base model provided well-predicted concentrations that corresponded to observed concentrations. However, the model seemed underpredicted with high observed concentrations.

Table 12. The comparisons of -2LL, AIC, BIC, and population pharmacokinetic parameter estimates in the residual error model selection process.

Residual error models	-2LL	AIC	BIC	PK parameter estimates					
				V (L/kg)	CV%	95% CI	CL (L/kg*h)	CV%	95% CI
Add	1011.464	1021.464	1040.52	0.616	7.83	0.521-0.711	0.125	8.34	0.104-0.145
Prop	796.726	806.726	825.782	0.699	7.68	0.594-0.805	0.137	7.99	0.116-0.159
Add with Prop	796.454	808.454	831.321	0.698	7.67	0.593-0.803	0.137	8.01	0.116-0.159

-2LL, twice negative log-likelihood; Add, additive, AIC, Akaike information criterion; BIC, Bayesian information criterion; CL, clearance; CV, confidence interval; Prop, proportional; V, volume of distribution.

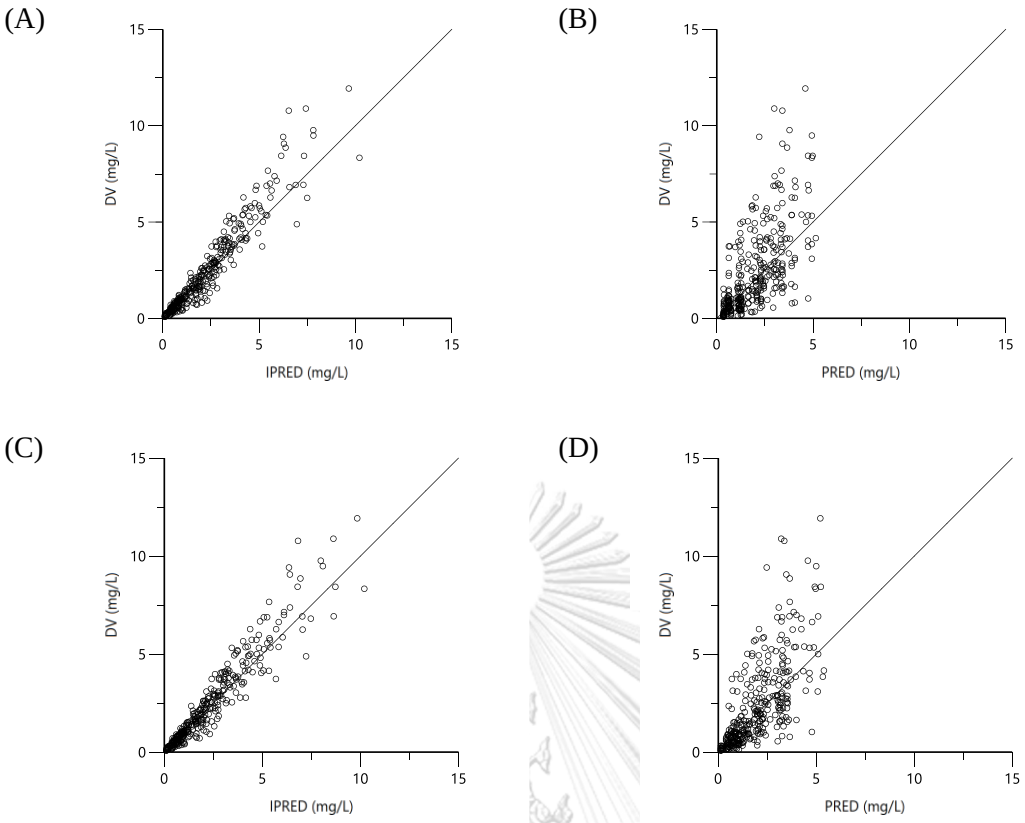


Figure 7. Goodness-of-fit plots (DV versus IPRED or PRED) for the base model and the final model.

Base model (A and B); final model (C and D); Observed concentrations (DV) versus individual-predicted concentrations (IPRED) (A and C); DV versus population-predicted concentrations (PRED) (B and D).

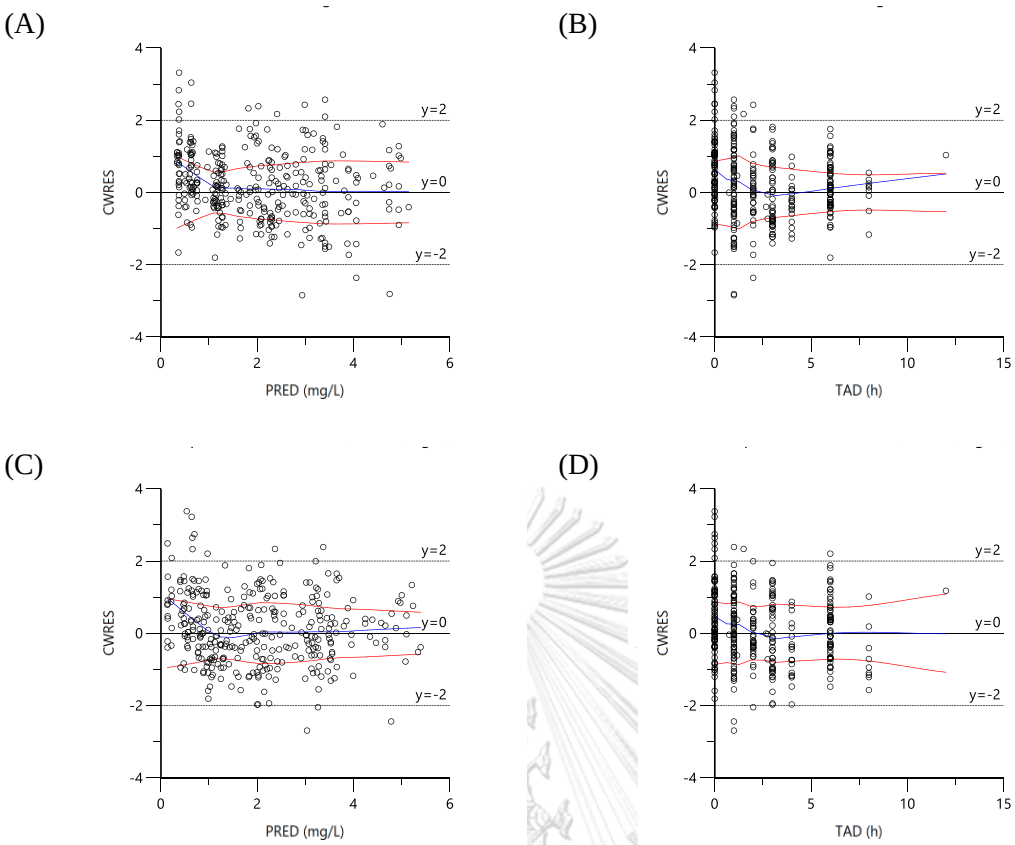


Figure 8. oodness-of-fit plots (CWRES versus PRED or TAD) for the base model and the final model.

Base model (A and B); final model (C and D); Conditional weighted residuals (CWRES) versus population-predicted concentrations (PRED) (A and C); CWRES versus time after dose (TAD) (B and D). The blue line is the trend line, and the red line is the trend line of absolute CWRES.

4.2.2. Covariate model and final model

The relationship between individual covariate values and random effect (η, Eta) of the volume of distribution and drug clearance was explored during the covariate search process. Box plots for categorical covariate and plots for continuous covariate versus Eta are shown in Figure 9. Of all covariates tested (age, sex, body weight, SCr, eGFR, Alb), V had a fair correlation with age, eGFR, and SCr; CL had a fair correlation with age and eGFR and a strong correlation with SCr. Alb and body weight were less likely to correlate with both V and CL. During the forward addition step, SCr and eGFR on CL reduced -2LL for >6.64. However, SCr on CL (CL-SCr) resulted in the most reduction of -2LL (32.147 versus 17.805). No further addition was found to reduce -2LL for >6.64. In the backward elimination step, SCr was removed from the model. It was found that -2LL was increased by 32.147 (>10.84). SCr effect on CL was retained in the final model. A summary of changes of -2LL during the forward addition and backward elimination steps is shown in Table 13.

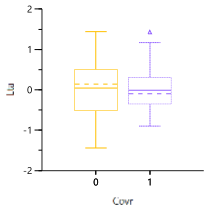
The relationship between V and CL was evaluated by covariance models. It was found that the non-diagonal model further reduced -2LL from 764.579 to 717.148. A summary of changes of -2LL, AIC, and BIC is shown in Table 14. The final population PK model is as follows:

$$\mathbf{CL\ (L/kg*h) = \theta_{CL} \times SCr^{\theta 1} \times exp\ (\eta_{CL})}$$

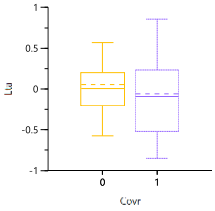
$$\mathbf{V\ (L/kg) = \theta_{V} \times exp\ (\eta_{V})}$$

where θ_V and θ_{CL} are the typical values of V and CL, respectively. θ_1 is the correction factor of SCr. The details of θ_V, θ_{CL}, and θ_1 are summarized in Table 15.

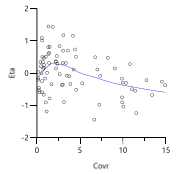
ηCL, Sex (0-female, 1 male)



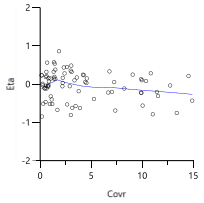
ηV, Sex (0-female, 1 male)



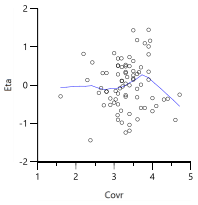
ηCL, Age (year)



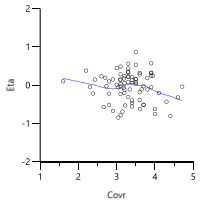
ηV, Age (year)



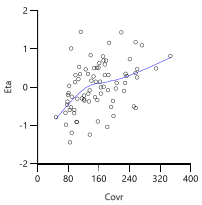
ηCL, Alb (g/dL)



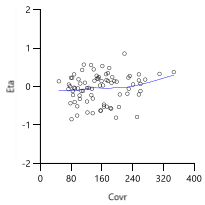
ηV, Alb (g/dL)



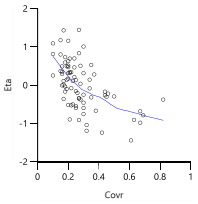
ηCL, eGFR (mL/min/1.73 m^2)



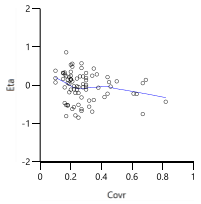
ηV, eGFR (mL/min/1.73 m^2)



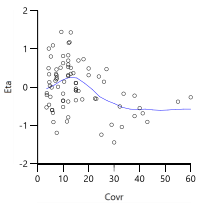
ηCL, SCr (mg/dL)



ηV, SCr (mg/dL)



ηCL, Body weight (kg)



ηV, Body weight (kg)

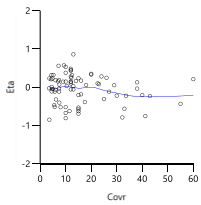


Figure 9. Scatterplots of the relationship between individual covariate values and random effect of drug clearance and volume of distribution during the covariate search process.

η or Eta, random effect; CL, drug clearance, V, volume of distribution.

Table 13. Forward addition and backward elimination steps of covariate model development.

Steps	Covariate added/subtracted	-2LL	Δ -2LL
cstep00	Base model	796.726	
First, find effect to add that reduces -2LL the most (>6.64)			
cstep01	V-Age	794.802	1.924
cstep02	CL-Age	794.322	2.404
cstep03	V-SCr	793.830	2.896
cstep04	CL-SCr	764.579	32.147
cstep05	V-eGFR	796.724	0.002
cstep06	CL-eGFR	778.921	17.805
Result: cstep04 CL-SCr was chosen.			
Second, find effect to add on CL-SCr that reduces -2LL the most (>6.64)			
cstep07	CL-SCr V-Age	762.735	1.862
cstep08	CL-SCr CL-Age	764.120	0.477
cstep09	CL-SCr V-SCr	761.552	3.045
cstep10	CL-SCr V-eGFR	764.317	0.28
cstep11	CL-SCr CL-eGFR	764.289	0.308
Result: No further effect chosen to add.			
Third, find effect to subtract that increases -2LL the least (<10.83)			
	CL-SCr	796.726	32.147
Result: No effect chosen to subtract. Final scenario to use was cstep04 CL-SCr.			

-2LL, twice negative log-likelihood; CL, clearance; eGFR, estimated glomerular filtration rate; SCr, serum creatinine; V, volume of distribution.

Remark: *At step cstep06, eGFR on CL significantly reduced -2LL for > 6.64 (17.805) but less than SCr on CL (32.147), Thus, SCr was selected.*

Table 14. Evalulation of covariance model.

Covariance models	-2LL	AIC	BIC
Diagonal	764.579	776.579	799.446
Non-diagonal	717.148	731.148	757.826

-2LL, twice negative log-likelihood; AIC, Akaike information criterion; BIC, Bayesian information criterion.

Table 15. Population pharmacokinetic parameter estimates of the final model and bootstrap.

Parameters	Base model parameters		Final model parameters		Bootstrap (N = 1000)		
	Estimate	%RSE	Estimate	%RSE	Median	2.5^{th} percentile	97.5^{th} percentile
θ_{CL}, L/kg*h	0.137	7.99	0.069	18.40	0.069	0.048	0.097
θ_V, L/kg	0.699	7.68	0.658	6.84	0.657	0.579	0.752
θ_1	NA	NA	-0.530	-20.75	-0.533	-0.753	-0.318
Interindividual variability							
ω^2_{CL} (shrinkage)	0.449 (6.33%)	19.60	0.337 (4.81%)	20.42	0.330		
ω^2_V (shrinkage)	0.233 (22.9%)	29.16	0.301 (10.44%)	21.92	0.295		
Residual variability							
σ_{prop}	0.319	7.71	0.306	6.72	0.304	0.265	0.341

CL, clearance; RSE, relative standard error; V, volume of distribution, θ_V, typical value of V; θ_{CL}, typical value of CL; θ_1, the correction factor of serum creatinine; ω^2_V, variance of interindividual variability for V; ω^2_{CL}, variance of interindividual variability for CL; σ_{prop}, residual error for the final model.

4.2.3. Model evaluation

4.2.3.1. Goodness-of-fit plots

The goodness-of-fit plots of the final model are shown in Figures 7 C, D and 8 C, D. Compared with the base model, the final model showed no obvious bias or significant trends within the plots of IPRED (Figure 7 C) and PRED (Figure 7 D) versus DV, and the data fitting was considerably improved. In the plots of CWRES versus PRED (figure 8 C) and TAD (figure 8 D), the majority of concentration data were distributed around 0 and within an acceptable range of -2 to +2, which indicated no significant systematic deviations in the model fitting.

4.2.3.2. Bootstrap

A 1000-run times bootstrap analysis was performed with no failure and demonstrated the robustness of the final PPK model. The parameter estimates from the original data set were similar to median values and within the 95% CI range of bootstrap results. A summary of the bootstrap details is shown in Table 15.

4.2.3.3. Prediction-corrected visual predictive check

A pcVPC of plasma colistin concentration versus TAD is shown in Figure 10. Most of the observed 5^{th}, 50^{th}, and 95^{th} quantiles distributed within the 90% CI of the predicted corresponding quantiles, indicating the precision of the final model. Overall, the evaluation of the colistin PPK model demonstrated that the final model provided a sufficient description of the data.

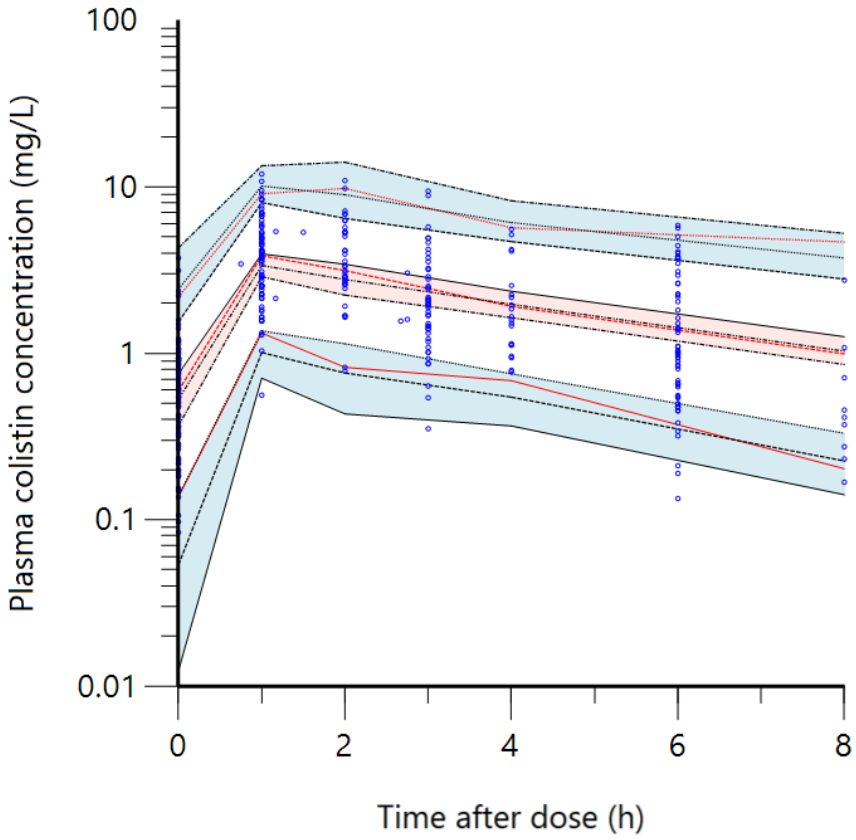


Figure 10. Prediction corrected-visual predictive check of the final model.
The observed colistin concentrations are shown as blue circles. Red solid line, dash line, and dot line represent the 5th, 50th, and 95th percentiles of the observed concentrations; the 3 shaded areas represent the 90% confidence interval for corresponding percentiles.

4.3. Pharmacodynamic assessment using simulation

All subsequent simulations were based on the validated final model. PPK parameter estimates, and variabilities were included in the simulation to create 10,000 replicates of virtual patients for each dosage regimen and SCr levels. The probability of target attainment (PTA) was predicted across the target $C_{ss,avg}$ of 0.25, 0.5, 1.0, 2.0, and 4.0 mg/L at the dosing schemes of 5, 7.5, 10, and 12.5 mg of CBA/kg/day divided into 12-h intervals with a 30-min intravenous infusion and 5 different SCr levels. The data and code for simulations are demonstrated in Appendix G and H. The results of % PTA are summarized in Table 16. It was demonstrated that the dose of 5 mg of

CBA/kg/day recommended by the US FDA and EMA would lead to an unacceptable PTA of less than 80% across all SCr ranges in this study when the target $C_{ss,avg}$ was 2 mg/L. Patients with lower SCr require a higher dose compared with those with higher SCr. However, with a lower target $C_{ss,avg}$ of ≤1 mg/L, colistin dose of 7.5 and 5 mg of CBA/kg/day were adequate for the patients with SCr levels of 0.1–0.3 and >0.3 mg/dL, respectively.

Table 16. Probability of target attainment of simulated patients with different serum creatinine levels who achieved target $C_{ss,avg}$ at different colistin dosing regimens (N = 10,000 replicates per clinical scenario).

Serum creatinine (mg/dL)	Colistin dose (mg CBA/kg/day)[a,b]	Probability of target attainment (%)				
		Target $C_{ss,avg}$ (mg/L)				
		0.25	0.5	1.0	2.0	4.0
0.1-0.20	5	99.6	93.1	61.1	18.2	1.7
	7.5	100	98.4	83.0	42.4	8.2
	10	100	99.7	93.3	61.3	18.8
	12.5	100	99.9	97.2	75.2	30.6
0.21-0.30	5	99.9	97.1	75.0	30.1	4.0
	7.5	100	99.5	90.8	57.0	16.2
	10	100	99.9	97.0	74.9	30.7
	12.5	100	100	98.9	86.1	45.0
0.31-0.40	5	99.9	98.5	82.6	40.2	7.1
	7.5	100	99.8	94.5	66.6	23.6
	10	100	100	98.2	82.7	40.2
	12.5	100	100	99.4	91.4	56.3
0.41-0.50	5	100	99.1	88.2	49.2	10.7
	7.5	100	99.9	96.7	74.3	31.1
	10	100	100	99.0	88.3	49.1
	12.5	100	100	99.7	94.4	64.6
0.51-0.75	5	100	99.6	93.6	63.0	19.4
	7.5	100	100	98.6	84.1	44.0
	10	100	100	99.7	93.7	62.9
	12.5	100	100	99.9	97.5	76.6

CBA, colistin base activity; $C_{ss,avg}$, average plasma colistin concentration at the steady-state.

[a] 30-min intravenous infusion per dose.

[b] divided into 12-h intervals.

Remark: *The median age of the study participants was 2.6 years (IQR, 0.8–6.8). Implementing data from this table to patients with the age outside the range described should be warranted.*

CHAPTER V DISCUSSION

This study aimed to describe the population pharmacokinetic parameters of formed colistin in pediatric patients and to investigate the probability of target attainment of various intravenous colistin doses to suggest the most appropriate regimen regarding the significant covariate. To the best of our knowledge, this is the largest study on this issue. Seventy-nine patients were enrolled in the analysis. Almost all of them were critically ill and admitted to ICUs. Two-thirds of them were treated with colistin for ventilator-associated pneumonia and one-thirds were treated for bloodstream infection. The currently recommended dose of colistin is insufficient when the initial target $C_{ss,avg}$ is 2 mg/L. Serum creatinine is the significant covariate of colistin apparent clearance. Thus, colistin in form of CMS should be prescribed according to SCr levels.

The one-compartment model with first-order elimination best described the PK behavior of intravenous colistin in pediatric patients, which is consistent with previous PPK studies in adults [17-21, 26, 27] and pediatrics [12, 73]. From the base model in this study, the typical value (mean) of CL was 0.137 L/kg*h. This was similar to previous pediatric studies of Wacharachaisurapol et al. [25] (0.15 L/kg*h, NCA analysis,), Ooi et al. [12] (0.123 L/kg*h, PPK analysis), and Antachopoulos et al. [73] (0.131 L/kg*h, PPK analysis). The typical value of V was 0.699 L/kg. This was similar to previous pediatric studies of Wacharachaisurapol et al (0.65 L/kg) and Ooi et al. (0.628 L/kg) but quite different from 1.38 L/kg reported from Antachopoulos et al. without a clear possible explanation.

Many PPK studies in adults reported that CrCL affected the apparent CL of formed colistin [17, 20, 21, 27, 43] even though it was mainly eliminated by non-renal pathways. This was also observed in a PPK study in pediatric patients [12]. The reason is that CMS, which is mainly eliminated by the renal pathway, is accumulated in patients with decreased CrCl. The excessive amount of CMS is more converted to formed colistin [9]. On the other hand, when kidney function is increased, formed colistin in plasma tends to have a lower level. For example, patients in Antachopoulos et al. [73] had a median eGFR of 130 mL/min/1.73 m^2 which was not different from our study of 140 mL/min/1.73 m^2. The probabilities to achieve the target $C_{ss,avg}$ of 2

mg/L by using a recommended dose of 5 mg of CBA/kg/day would be only 41.2% and 30.1−40.2%, respectively. Blood urea nitrogen, a kidney function biomarker, was also identified as a covariate of colistin apparent CL in one adult study [26]. It is not surprising that SCr was inversely associated with colistin CL in this study. Even though both of SCr and eGFR (or CrCl) affected colistin clearance (Table 13), SCr was selected as the significant covariate and remained in the final model regarding the statistical (-2LL) criteria. Greater statistical significance of SCr compared with eGFR influencing colistin apparent CL in this study potentially regarding the eGFR calculating method. Even though the most widely used eGFR calculation in pediatrics is the modified ("bedside") Schwartz equation: 0.413 × (height/SCr) [28], there are several limitations to using this bedside equation. First, this equation was evaluated in children with a median age of 10.8 years (IQR, 7.7–14.3). This age range was different from our participants with a median age of 2.6 years (IQR, 0.8–6.8). Differences in age range might affect baseline SCr levels that are with respect to body mass. Older children, especially >7 years, have a higher normal SCr level with less variability compared with younger children and infants (Table 4). Second, the equation evaluated was from the data of children with mild to moderate chronic kidney disease with a median SCr level of 1.3 mg/dL (IQR, 1.0–1.8) resulted in a low median GFR of 41.3 mL/min/1.73 m^2 (IQR, 32.0–51.7) compared with a median SCr of 0.25 mg/dL (IQR, 0.19−0.32) and median eGFR of 147.8 mL/min/1.73 m^2 (IQR, 102.5−186.9) reported from the current study. Schwartz and colleagues also suggested that their formula needed to be validated in children with higher GFR to confirm the generalizability. A further issue to be concerned about is that the inaccurate height or length measurement made calculated eGFR less reliable. Measuring height or length in critically ill pediatric patients in bed or infants and young children <2 years of age in lying position could cause inaccurate results [74, 75]. Compared with eGFR, SCr is more straightforward and less interfered with by another factor because it is measured directly in a blood sample. SCr level is correlated with age, body mass, and kidney function. Different SCr levels in patients of the same age range reflect different kidney functions.

Low SCr level may occur regarding pathophysiologic changes such as augmented renal clearance (ARC). ARC was found in up to 10–67% of critically ill pediatric

patients [76-78]. The ARC could cause enhanced excretion of serum creatinine and drugs owing to glomerular hyperfiltration. Patients with a very low SCr potentially have low plasma colistin concentrations regarding this reason.

The volume of distribution of formed colistin was related to body weight reported from pediatric PPK studies [12, 73]. It was found that younger children with a higher volume of distribution had lower plasma colistin levels [25]. However, the association of age and volume of distribution could not be demonstrated in this study. The possible explanations are that the majority of patients in the current study were young children and the range of body weight may not different enough to demonstrate the effect on the volume of distribution. We also used colistin dose which was normalized by body weight in the modeling process. The plausibility of body weight on PK parameters was diminished and made the final model simpler.

The ratio of the AUC of the unbound colistin concentration in plasma across 24 h to MIC is the PK/PD index that correlates with the bacterial killing property [11]. $C_{ss,avg}$ of 2 mg/L has been proposed as an initial target concentration for bloodstream and some other infections when the colistin MIC is ≤2 mg/L [17]. This target also seems appropriate for pediatric patients [12]. The US FDA and EMA recommended colistin dose in children of 2.5–5 mg of CBA/kg/day [40, 41]. From the simulation, 18.2–63.0% of simulated patients with a colistin dose of 5 mg of CBA/kg/day achieved the target $C_{ss,avg}$ of 2 mg/L. Ooi et al. [12] conducted a PPK study in 5 pediatric patients with a median age of 1.75 years (range 1.25 months to 6.25 years) receiving colistin 6.6 mg of CBA/kg/day. The median $C_{ss,avg}$ was only 0.88 mg/L, with wide interindividual variability. More recently, Antachopoulos et al. [73] published a PPK study of 17 critically ill pediatric patients with a median age of 3.3 years (range 3 months to 13.75 years). The colistin doses were 6.6 mg of CBA/kg/day in 6 patients, 9.9 mg of CBA/kg/day in 10, and 11.6 mg of CBA/kg/day in one. The $C_{ss,avg}$ was 1.11–8.47 mg/L (median 2.92 mg/L). Only ten (58.8%) patients achieved $C_{ss,avg}$ of ≥2 mg/L. The data from the current study, together with the data from Ooi et al. and Antachopoulos et al., are evidence that the current colistin dose recommendation of 2.5–5 mg of CBA/kg/day for pediatric patients is subtherapeutic. However, colistin is almost always prescribed in a combination of antibiotics regarding the recommendations [17, 79]. All patients

reported in Study 3 were prescribed colistin with at least one concomitant antibiotic; meropenem was the majority of 70%. The 30-day mortality rate was only 11.0% [80] and within the range of 7.1–29.3% reported from other pediatric studies [5, 12, 43-46, 53, 55]. *In vitro* studies demonstrated synergistic effects of carbapenems and colistin against carbapenem-resistant *A. baumannii* (meropenem + colistin) and carbapenem-resistant *K. pneumoniae* (doripenem + colistin) [81, 82]. Combination of doripenem and colistin at the highest dosage regimens also suppressed colistin-resistant and colistin-heteroresistant strains of *K. pneumoniae*. However, treating MDR-GNB with a higher colistin MIC of >2 mg/L, the other antibiotics such as amikacin (if sensitive), or a new antibiotic like cefiderocol might be a preferable option.

Since $C_{ss,avg}$ of <2 mg/L might be appropriate when the MIC of the target pathogen is <2 mg/L in bloodstream infection or <1 mg/L in lung infection. Local epidemiology and colistin MIC distribution of common MDR-GNB are crucial data to guide the appropriate target of the individual institution. The actual MIC by a proper method (e.g., broth microdilution) should be obtained. Dose adjustment could be considered following the recommendations from this study (Table 12). For example, during 2019–2020, 45 clinical isolates of *A. baumannii* from KCMH pediatric patients were obtained for colistin MIC (unpublished internal data). The MIC distribution was: <0.5 mg/L, 26.6%; 0.5 mg/L, 33.3%; 1 mg/L, 22.2%; 2 mg/L, 13.3%; >2 mg/L, 4.4%. The initial target $C_{ss,avg}$ of 1 mg/L would be appropriate. At this target $C_{ss,avg}$, the initial dose of 7.5 mg of CBA/kg/day might be adequate for patients with a SCr of 0.1–0.3 mg/dL while 5 mg of CBA/kg/day might be adequate for patients with higher SCr values. A concern for using a higher dose of colistin is potential nephrotoxicity. However, nephrotoxicity was less observed in pediatric patients compared with adults. Some pediatric studies used a higher dose of colistin. Iosifidis et al. [54] conducted a retrospective study of 13 pediatric patients using 19 colistin courses. High dose colistin (6.6–7.5 mg of CBA/kg/day) was used in 5 courses without nephrotoxicity (nephrotoxicity definition: elevation of SCr values beyond the estimated normal range for the patient's age group). None experienced AKI in Ooi et al. [12]. One out of 17 patients in Antachopoulos et al. [73] who was administered with colistin 9.9 mg of CBA/kg/day had an elevated SCr level. However, the author concluded that kidney

impairment in this patient might occur regarding the patient's comorbidity of rapidly progressing Burkitt lymphoma. This patient was also administered with concomitant nephrotoxic agents (gentamicin and teicoplanin).

The application of dose suggestion (Table 16) from this study should be warranted in patients outside the age range of study participants. The reason is that the dose suggestion from the current study is with respect to SCr levels. Number of participants classified by age groups together with a median (IQR) of baseline SCr showing in Table 10 revealed that two-thirds of participants were 1 month to 7 years of age and shared a similar normal range of SCr. Thus, altered SCr level indicated different kidney functions that directly affected colistin apparent CL. Patients with a higher SCr may require a lower dose of colistin. On the other hand, older children, especially >7–15 years of age, have higher normal SCr levels. This could also be observed in our study participants (Table 10). For example, a 12-year-old patient with a SCr of 0.6 mg/dL should have a normal kidney function while a 2-year-old patient with the same SCr level may have an impaired kidney function. In this case, the older patient may require a higher dose of colistin compared with the younger patient with the same SCr level.

Dose suggestion also could not be applied for neonates owing to this study did not include those populations even though the colistin dose of 5 mg of CBA/kg/day was also subtherapeutic for neonates reported from Nakwan et al. [15]. Subtherapeutic plasma colistin levels in neonates may cause by a high volume of distribution in accordance with the high total body water of this population. The supporting evidence was the longer elimination half-life of colistin regarding CMS and/or formed colistin distributed from the circulation and needed a period of time to re-enter the circulation. The other reason is that the immaturity of hydrolysis enzymes, mainly blood esterases, of the neonates compared with older children and adults. This may cause delayed conversion of CMS into formed colistin.

Further studies for the specific populations are required. Patients with less severe infections such as UTI without sepsis might need different colistin regimens compared with our recommendation owing to almost all of the patients in this study is critically ill. Critically ill patients have altered pharmacokinetics regarding their

pathophysiologic changes [83]. When applicable, the therapeutic drug monitoring of plasma colistin should be performed to guide the appropriate dose and to avoid nephrotoxicity related to the excessive dose of colistin. While using a higher dose, adverse drug reactions especially nephrotoxicity should be monitored. Nephrotoxicity caused by colistin mostly occurs within the first week after colistin initiation.

Administering a loading dose of colistin is now a standard of care recommended in adults [17, 84]. Without this approach, it might take many hours or even days for colistin to achieve the steady-state level, especially in critically ill patients [18, 20]. No recommendation of using colistin loading dose is suggested in pediatric patients [40, 41]. In children, it was found that colistin treatment without a loading dose may have an association with mortality [85]. A small PPK study demonstrated that plasma colistin concentration reached the steady-state within 12–24 h after initiation without a loading dose [12]. From our previous PK study (study 1, [25]) of an intravenous colistin loading dose, the median average concentration after giving a loading dose of 4 mg of CBA/kg achieved the target level of ≥2 mg/L which improved the drug exposure [25]. Moreover, giving a colistin loading dose did not increase the AKI risk (Table 10). This strategy is reasonable to apply to pediatric patients.

The method of formed colistin determination was successfully developed regarding the Bioanalytical Method Validation Guidance for Industry under the recommendation of the U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Veterinary Medicine (CVM) [86]. Even though it was an in-house development method, it has met all requirements of validation. Colistin determination has a great potential to be implemented in clinical services soon. This would be beneficial for therapeutic drug monitoring especially in the patients who need to receive a higher dose of colistin.

Our study has several strengths. First, we started with a full PK study in pediatric patients and gained initial knowledge of colistin PK characteristics and the PK benefit of giving a colistin loading dose. The knowledge we gained was used as the basis for the current study. A larger study population with a broader age range into infancy was conducted. More sophisticated PK method like population pharmacokinetic analysis

was applied to gain more understanding in pediatric patients. A significant covariate was identified and dose simulation regarding this was successfully performed. A higher dose of colistin is necessary especially in patients with low SCr levels. The knowledge of colistin-associated nephrotoxicity was explored in a larger pediatric population. It was found that administering a colistin loading dose did not increase the AKI risk.

This study also has some limitations. In Study 2, even though the multicenter collaboration was beneficial in higher rates of patient enrolment, heterogeneity among centers might affect the internal validity. Furthermore, colistin used among the clinical centers was not from the same manufacturer. Sensitivity analysis was done and confirmed that they were similar. In Study 3, the study participants came from all 20 patients from Study 1, 15 KCMH patients from Study 2, and 146 KCMH patients outside Study 1 and 2 to form a larger data set. No data from QSNICH on nephrotoxicity was included. However, the results of Study 3 could probably be generalized regarding both clinical centers were the same level of tertiary care settings. The findings from this study could not be generalized to the age groups outside the study population: neonates might have different pharmacokinetic patterns; adolescents have higher normal SCr values compared with the majority of patients in this study. The application of dose recommendation in this study also should be warranted in non-critically ill patients regarding almost all patients in this study were critically ill and might have different pharmacokinetics. Patients with severe kidney impairment or who underwent renal replacement therapy did not include in this study, the appropriate dose for those patients could not be recommended. Proposed higher recommended doses and their association with efficacy and safety were not explored. There are some challenges in clinical practice also. Colistin MIC that is necessary for determining the target $C_{ss,avg}$ could be performed only in some advanced reference microbiology laboratories. Plasma colistin level determination requires a sophisticated machine and experienced personnel. However, if a good system and logistics were set, samples shifting to the reference centers would be possible.

The remaining research gaps that are needed to be explored include (i) the efficacy and safety of higher recommended doses from the simulations in children (ii) the appropriate dose of colistin for the special populations such as neonates, pediatric

patients with impaired kidney function, or those who underwent organ support machines (RRT, ECMO), (iii) the role of colistin therapeutic drug monitoring.

In conclusion, we successfully developed a population pharmacokinetic model of intravenous colistin in pediatric patients. Serum creatinine level is a significant covariate on colistin clearance. Simulations based on the final model revealed that the currently recommended dose of 5 mg of CBA/kg/day is subtherapeutic when the target $C_{ss,avg}$ is ≥2 mg/L. For the target $C_{ss,avg}$ of ≤1 mg/L, this dose might be adequate only for the patients with SCr level of >0.3 mg/dL, and a higher dose of 7.5 mg of CBA/kg/day might be required for the patients with lower SCr levels.

Appendix A: The methodology of study 3 (No Increased Acute Kidney Injury Rate Through Giving an Intravenous Colistin Loading Dose in Pediatric Patients)

Study design

This retrospective study was conducted at King Chulalongkorn Memorial Hospital, Bangkok, Thailand. Pediatric patients who were prescribed intravenous colistin were identified by searching the pharmacy unit database. Generic names of colistin (colistin, colistimethate sodium, colistin methanesulfonate, CMS) were used for searching the patients aged ≤18 years during the period of January 2014 and December 2019. Eligibility criteria included (i) age 1 month to 18 years, (ii) receiving intravenous colistin ≥48 h and (iii) having baseline serum creatinine (SCr) result and interval follow−up during day 3–7 after prescribing colistin. Premature infants <37 weeks and those receiving renal replacement therapy (RRT) or extracorporeal membrane oxygenation (ECMO) prior to colistin initiation were excluded. This study was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University (IRB no. 177/63).

Definitions

Colistin loading dose was defined as a CMS intravenous injection of at least 4–5 mg of colistin base activity (CBA)/kg/dose. Baseline SCr was defined as a SCr within 48 h before colistin initiation. Follow−up SCr was defined as a SCr at day 3–7 after colistin initiation and weekly SCr for 3 further consecutive weeks (if available). If there were more than one SCr value in the period, the highest SCr value was chosen. All SCr was measured by the enzymatic method at the clinical pathology laboratory, King Chulalongkorn Memorial Hospital. The eGFR was calculated by using the modified Schwartz equation: $eGFR = k \times Ht/SCr$, $k = 0.413$ for all patients. In patients with eGFR ≥80 mL/min/1.73 m^2, AKI was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) SCr criteria. Stage 1 AKI was defined as an increase of follow−up SCr >1.5–1.9 times of baseline. Stage 2 AKI was defined as an increase of follow−up SCr >2.0–2.9 times of baseline. Stage 3 AKI was defined as an increase of

follow−up SCr >3 times of baseline or necessary to receive RRT. Urine output criteria were not applied in this study regarding the less reliability of the documentation retrospectively and drug−induced AKI is unlikely to cause oliguria (Miano et al., 2018). In infants and young children with the age of 1 month to 2 years which are at risk population for AKI, pRIFLE criteria which are more sensitive (Sutherland et al., 2015) were also used for AKI diagnosis and compared with KDIGO SCr criteria. In patients with eGFR <80 mL/min/1.73 m^2 who were considered having impaired kidney function before colistin initiation were considered to have deteriorated kidney function when the follow−up SCr increased >1.5 times of baseline. Augmented renal clearance (ARC) was defined as a baseline eGFR >150 mL/min/1.73 m^2 (Van Der Heggen et al., 2019). In patients who developed AKI, the recovery from AKI was considered when the follow−up SCr was <1.5 times of baseline.

Antibiotic resistance pattern was reported as multidrug resistance (MDR) defined as resistance to ≥3 classes of antibiotics; extensive drug resistance (XDR) defined as resistance to all but one or two classes of antibiotics; pandrug resistance (PDR) defined as resistance to all antibiotics tested; carbapenem resistance (CR) defined as resistance to at least one carbapenem and was reported separately from MDR, XDR, and PDR patterns. Colistin MIC was performed by Etest (bioMérieux, Marcy l'Étoile, France) at Microbiology unit, King Chulalongkorn Memorial hospital.

Empirical treatment was defined as a colistin prescribing indication according to the clinical syndromes and before knowing microbiological data. Targeted treatment was defined as a colistin prescribing indication according to the known microbiological result of MDR−GNB. Thirty−day mortality was defined as death from any cause occurring within 30 days after colistin initiation. Patients who were discharged before 30 days were considered as alive.

Data collection and management

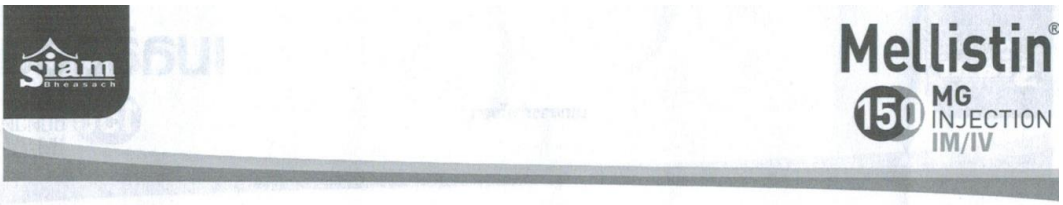
A case record form was created for study purposes. All medical records of the identified cases were reviewed by the investigators. Patients' data including demographics, colistin indication, colistin dosing, serial SCr (baseline and follow−up), microbiological data, and treatment outcomes (renal replacement therapy and 30−day

mortality) were extracted manually from electronic medical records to the case record forms.

Data analysis

Categorical variables were analyzed with Pearson's Chi–square test or Fisher's exact test, as appropriate, and are presented as counts and percentages. Continuous variables were analyzed with t–test and are presented as mean with 95% confidence interval (CI) and/or median with interquartile ranges (IQR). Factors associated with AKI were assessed using univariable and multivariable logistic regression and are presented using odds ratios and 95% CI with *P*–values of Z–test. Factors with an association of $P < 0.1$ in univariable analysis were selected for further multivariable analysis. The interested different initial doses of colistin treatment were included in the multivariable model for adjusting the association with AKI. Stata/SE version 13.0 was used for all data analyses.

Appendix B: Colistin package inserts



MELLISTIN 150 MG INJECTION

Name and strength of active ingredient :-

Each vial contains Colistimethate sodium equivalent to Colistin 150 mg

Each gram of Colistin contains sodium 0.099 mg (0.0043 mmol)

Product description :-

White to almost white sterile powder for reconstitution for injection

Properties :-

Pharmacodynamics :

Colistimethate sodium is the sulfamethyl derivative of Colistin. Colistin or Polymyxin E is a Polymyxin antibiotic obtained from *Bacillus polymyxa var. Colistinus* that is active against many gram-negative bacilli and inactive against gram-positive bacteria, fungi, and viruses. The mechanism of action is bactericidal. Colistimethate (Colistin-methanesulfonate) is hydrolyzed to Colistin which acting like a cationic detergent and binds to the bacterial cytoplasmic membrane of susceptible bacteria. This alters permeability and causes leakage of bacterial cell wall. This leads to bacterial death. In vitro, Colistin is active against these bacteria as follows

Aerobic gram-negative bacteria

Acinetobacter sp., *Acinetobacter baumannii*, *Citrobacter* sp., *Escherichia coli*, *Enterobacter aerogenes*, *Haemophilus influenza*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Salmonella* sp., *Shigella* sp. And some strains of *Bordetella* sp., *Vibrio* sp.

Some bacteria have been reported resistance to Colistin. Those are *Proteus* sp., *Providencia* sp., *Serratia* sp., *Neisseria gonorrhoeae*, *N. meningitidis*, and *Bacteriodes fragilis*.

Pharmacokinetics :

Colistimethate sodium is not absorbed from the GI tract and must be given parenterally. The drug is widely distributed into body tissues such as the liver, kidneys, lung, heart, and muscle. In patients with normal or inflamed meninges, only minimal concentrations of antimicrobial activity are attained in cerebrospinal fluid (CSF). More than 50% of Colistin bound to serum proteins. It also crosses the placenta and is distributed into milk. Colistimethate sodium is hydrolyzed to Colistin and possibly other metabolites with fewer substituted amino groups. The plasma half-life of Colistimethate sodium is 1.5-8 hours in adults with normal renal function and is prolonged in patients with impaired renal function. Both Colistimethate sodium and metabolites of the drug are excreted mainly by the kidneys.

Colistimethate sodium may be removed by hemodialysis and, to a lesser extent, by peritoneal dialysis.

Indication :-

Colistimethate sodium is used parenterally for the treatment of acute or chronic infections caused by certain susceptible gram-negative bacilli such as *Acinetobacter baumannii* (including *Acinetobacter baumannii* which resistant to all antibiotics), *Pseudomonas aeruginosa* (including *Pseudomonas aeruginosa* which resistant to all antibiotics), *Escherichia coli* (including ESBL-producing *Escherichia coli*), *Klebsiella pneumoniae* (including ESBL-producing *Klebsiella pneumoniae*), *Enterobacter aerogenes*, *Citrobacter* sp., *Haemophilus influenza*, *Salmonella* sp., *Shigella* sp., *Proteus* sp., *Providencia* sp., *Serratia* sp. and some strains of *Bordetella* sp., *Vibrio* sp. Colistimethate sodium is administered by oral inhalation via nebulization for the treatment of *Pseudomonas aeruginosa* in respiratory tract infections among patients with cystic fibrosis.

Mode of administration :-

MELLISTIN 150 MG injection is administered by IM injection, IV injection, continuous IV infusion or oral inhalation.

With concern of microbial contamination, the drug should be used promptly after the preparation and the remaining mixed solution should be discarded.

Color changing or any precipitation should be observed before use.

Preparation for intramuscular (IM) and intravenous (IV) injection

MELLISTIN 150 MG injection is reconstituted by adding 2 ml of sterile water for injection to a vial, the resultant solution contains 75 mg of Colistin per ml. The vial should be swirled gently to avoid frothing.

The drug should be injected directly into a vein over 3-5 minute period every 12 hours.

Preparation for intravenous (IV) infusion

For continuous IV infusion, one-half of the total daily dose should be injected directly into vein over 3-5 minute period every 12 hours. The remaining one-half of the total daily dose should be added to a compatible IV solutions as the following; 0.9% sodium chloride injection, 5% dextrose, 5% dextrose and 0.225% sodium chloride injection, 5% dextrose and 0.45% sodium chloride injection, 5% dextrose and 0.9% sodium chloride injection, lactated Ringer's solution or 10% invert sugar. Swirl gently to avoid frothing.

Intravenous (IV) infusion administration

The drug should be administered 1-2 hours after the initial dose by slow IV infusion over the next 22-23 hours. The infusion rate should be 5-6 mg/hour in patients with normal renal function. For patients with impaired renal function, the infusion rate should be reduced depending on the degree of renal impairment.

Preparation for oral inhalation

For oral inhalation via nebulization, an isotonic solution of Colistimethate sodium has been prepared by diluting the appropriate dose in 2-4 ml of preservative-free 0.9% sodium chloride injection or sterile water and should be used promptly after being prepared.

Stability

Following reconstitution with sterile water for injection, Colistimethate sodium solutions containing 75 mg of Colistin per ml should be stored at 2-8°C or 25°C and used within 10 days. For the reconstitution with 0.9% NSS or D5W, Colistimethate sodium solutions containing 1.5 mg of Colistin per ml should be stored at 2-8°C or 25°C and used within 72 hours. **However, Solutions of Colistimethate sodium should be used promptly after being mixed.**

Recommendation dose :-

Dosage and administration depend on severity of infection, patient status, renal function, and causative organism or follow physician's instruction.

The usual IM or IV dosage of Colistimethate sodium for adults and children with normal renal function is 2.5-5 mg/kg of Colistin daily given in 2-4 divided doses.

The maximum IM or IV dosage of Colistimethate sodium is 5 mg/kg of Colistin daily.

For early treatment of *Pseudomonas aeruginosa* respiratory infections in adults and pediatric cystic fibrosis patients, Colistimethate sodium has been given by oral inhalation via nebulization in a dosage of 33.33-66.66 mg of Colistin 2 or 3 times daily.

Dosage in renal impairment

In patients with renal impairment, the dose and frequency of Colistimethate sodium should be decreased in proportion to the degree of renal impairment.

Suggested modification of Colistimethate dosage schedules for adults with impaired renal function

Renal fuction	Normal	Mild	Moderate	Severe
Serum creatinine (mg/dL)	0.7-1.2	1.3-1.5	1.6-2.5	2.6-4
Urea clearance (% of normal)	80-100	40-70	25-40	10-25
Dose (mg)	100-150	75-115	66-150	100-150
Frequency (times per daily)	2-4	2	1 or 2	q 36 hr
Total daily dose (mg)	300	150-230	133-150	100
Approx. daily dose (mg/kg/day)	5	2.5-3.8	2.5	1.5

Contraindication :-

Colistimethate sodium is contraindicated in individuals who are hypersensitive to the drug or Polymyxins.

Warning and Precaution :-

Warning :

1. Colistimethate sodium is contraindicated in individuals who are hypersensitive to the drug.
2. Colistimethate sodium may cause transient neurological disturbances and nephrotoxicity.

Precaution :

1. Maximum dosage: Do not exceed 5 mg/kg/day in patients with normal renal function
2. Colistimethate sodium may cause nephrotoxicity, manifested as decreased urine output, increased serum concentrations of BUN and creatinine, proteinuria, hematuria, and casts in the urine. If these symptoms occur, dosing should be adjusted or the drug should be discontinued immediately.
3. Colistimethate sodium may cause transient nervous system effect, including circumoral or peripheral paresthesia or numbness, tingling or formication of the extremities or tongue, dizziness, vertigo, giddiness, ataxia, blurred vision, and slurred speech. These adverse nervous system effects generally appear within the first 4 days of therapy and disappear when the drug is discontinued. The patient should be monitored closely; some of these adverse nervous system effects may be alleviated by reducing dosage of the drug.
4. Treatment with Colistimethate sodium alters the normal flora in the gut leading to overgrowth of *Clostridium difficile*. *C. difficile* produces toxins which contribute to the development of CDAD that must be considered in all patients who present with diarrhea following Colistimethate sodium use. Mild cases of colitis may respond to discontinuance of the drug alone, but management of moderate to severe case should include treatment with fluid, electrolyte, protein supplementation, and appropriate anti-infective therapy.
5. Since nephrotoxic effects may additive, concurrent or sequential use of Colistimethate sodium with other drugs which have similar toxic potentials and with neuromuscular blocking agents should be avoided.
6. Patients who received Colistimethate sodium by oral inhalation via nebulization may cause bronchoconstriction. It has been suggested that premedication with bronchodilators may reduce the potentials for development of bronchoconstriction.

Interactions with other medicaments:-

1. Since nephrotoxic effects may additive, concurrent or sequential use of Colistimethate sodium and other drugs with similar toxic potentials (e.g., aminoglycosides, amphotericin B, capreomycin, cephalothin, methoxyflurane, polymyxin B sulfate, vancomycin) should be avoided, if possible.
2. Neuromuscular blocking agents (e.g., tubocurarine, succinylcholine, ether, decamethonium, gallamine) and other drugs (e.g., sodium citrate) potentiate neuromuscular blockade. These drugs should be used with extreme caution in patients receiving Colistimethate sodium.

Pregnancy and lactation :-

There are no adequate and well-controlled study in pregnant women. Use during pregnancy only when the potential benefits justify the possible risks to the fetus.

It is not known whether Colistimethate sodium is distributed into milk. The drug should be temporarily discontinue during nursing administration.

Undesirable effects :-

Adverse reactions which may occur during the use of the drug are

Renal effects: nephrotoxicity, manifested as decreased urine output, increased serum concentrations of BUN and creatinine, proteinuria, hematuria, and casts in the urine

Nervous system effects: circumoral or peripheral paresthesia or numbness, tingling or formication of the extremities or tongue, dizziness, vertigo, giddiness, ataxia, blurred vision, and slurred speech

Respiratory effects: Respiratory arrest, Apnea, Bronchoconstriction, Respiratory distress

Other adverse effects: generalized pruritus or urticaria, rash, drug fever, dysphonia, and pain at the site of injection. Moreover, leucopenia and granulocytopenia may be found (rare).

Overdosage and treatment :-

Overdosage of Colistimethate sodium can cause neuromuscular blockade characterized by paresthesia, lethargy, confusion, dizziness, ataxia, nystagmus, disorder of speech, apnea, respiratory muscle paralysis, respiratory arrest, and death. Overdosage of the drug may also cause acute renal failure, manifested as decreased urine output and increase in serum concentrations of BUN and creatinine.

Treatment for overdosage : The drug should be discontinued and initiate supportive treatment.

Colistimethate sodium may be removed by hemodialysis and, to a lesser extent, by peritoneal dialysis.

Storage condition :-

Keep out of reach of children.

Dry powder should be kept below 30°C before reconstitution.

Do not freeze the solution.

Dosage forms and packaging available :-

Sterile powder for injection is contained in clear colorless glass vial (glass type III) with grey chlorobutyl rubber and aluminium cap. Each vial contains sterile powder equivalent to Colistin 150 mg. It may contain 1, 5, 10, 20, 30, 50, and 100 vials per box.

Update : (13/11/2017)

Manufacturer :-

Siam Bheasach Co., Ltd.

123 Soi Chokechai Ruammitr, Vibhavadi-Rangsit Rd., Chomphon, Chatuchak, Bangkok 10900, Thailand and 9 Soi Chokechai Ruammitr 3, Vibhavadi-Rangsit Rd., Dindang, Dindang, Bangkok 10400, Thailand

Distributor :-

Siam Pharmaceutical Co., Ltd.

171/1-2 Soi Chokechai Ruammitr, Vibhavadi-Rangsit Rd., Chomphon, Chatuchak, Bangkok 10900, Thailand

Tel. 02-6259999

MELL-150-03-L-THAI-ENG-A0004

Siam Bheasach

เมลลิสติน 150 มก. ชนิดฉีด IM/IV

เอกสารกำกับยา

เมลลิสติน 150 มก. ชนิดฉีด
MELLISTIN 150 MG INJECTION

ชื่อและความแรงของตัวยาสำคัญ :-
ใน 1 ขวด ประกอบด้วยยาสำคัญ คือ Colistimethate sodium ผสมผสมกับ Colistin 150 มิลลิกรัม
ในแต่ละกรัมของ Colistin ประกอบด้วยโซเดียม 0.099 มิลลิกรัม (0.0043 มิลลิโมล)

ลักษณะของผลิตภัณฑ์ :-
ผงยาปราศจากเชื้อสีขาวถึงขาวนวล สำหรับละลายเพื่อใช้ฉีด

คุณสมบัติ :-

เภสัชพลศาสตร์ :
Colistimethate sodium เป็นอนุพันธ์ sulfamethyl ของ Colistin ซึ่ง Colistin หรือ polymyxin E จัดเป็นยาปฏิชีวนะกลุ่ม polymyxins ที่สร้างจากเชื้อแบคทีเรีย *Bacillus polymyxa var. colistinus* ซึ่งมีประสิทธิภาพในการฆ่าเชื้อ gram-negative bacilli หลายชนิดและไม่มีผลต่อแบคทีเรียแกรมบวก เชื้อราและไวรัส กลไกการออกฤทธิ์ของยาเป็นการออกฤทธิ์ทำลายเชื้อ (bactericidal) มีดังนี้ Colistimethate (Colistin-methanesulfonate) จะถูก hydrolyzed เป็น Colistin ซึ่งมีคุณสมบัติเป็น cationic detergent โดยจะทำปฏิกิริยากับ bacterial cytoplasmic membrane โดยการขับกับหนังเซลล์ของแบคทีเรีย ส่งผลต่อการรีมผ่านของหนังเซลล์ของแบคทีเรีย ทำให้หนังเซลล์รั่วและแบคทีเรียตายในที่สุด ในหลอดทดลอง Colistin ออกฤทธิ์ต่อเชื้อแบคทีเรีย ดังนี้

แกรมลบชนิดที่ไวต่อยาดังนี้
Acinetobacter sp., Acinetobacter baumannii, Citrobacter sp., Escherichia coli, Enterobacter aerogenes, Haemophilus influenza, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella sp., Shigella sp. และบางสายพันธุ์ของ *Bordetella sp., Vibrio sp.*
เชื้อที่ดื้อต่อ Colistin ได้แก่ *Proteus sp., Providencia sp., Serratia sp., Neisseria gonorrhoeae, N. meningitidis, Bacteriodes fragilis*

เภสัชจลนศาสตร์ :
Colistimethate sodium ไม่ถูกดูดซึมจากทางเดินอาหาร ต้องให้โดยการฉีดเท่านั้น ยาสามารถแพร่กระจายเข้าสู่เนื้อเยื่อต่าง ๆ ของร่างกายได้ดี เช่น ตับ ไต ปอด หัวใจ และกล้ามเนื้อ แต่แพร่กระจายเข้าสู่น้ำในช่องไขสันหลังและสมอง (CSF) ได้เพียงเล็กน้อย ทั้งกรณีที่เกิดการอักเสบในเยื่อหุ้มสมองและในกระเยื่อหุ้มสมองปกติ ยาขับกับโปรตีนในพลาสมามากกว่า 50% Colistin สามารถแพร่ผ่านทางรกและทางน้ำนมได้ Colistimethate sodium จะถูก hydrolyzed เป็น Colistin และมีบางส่วนถูกเมแทบอไลซ์โดยการแทนที่หมู่อะมีโน ค่าครึ่งชีวิตของ Colistimethate sodium ในผู้ใหญ่ไตปกติประมาณ 1.5-8 ชั่วโมง และจะมีค่าครึ่งชีวิตยาวนานขึ้นในผู้ใหญ่ไตบกพร่อง ทั้ง Colistimethate sodium และเมแทบอไลต์จะถูกขับออกจากร่างกายทางไตเป็นส่วนใหญ่ Colistimethate sodium สามารถขจัดออกจากร่างกายโดยวิธี hemodialysis แต่วิธี peritoneal dialysis สามารถขจัดยาออกจากร่างกายได้น้อยกว่า

ข้อบ่งใช้ :-
ใช้รักษาการติดเชื้อในส่วนต่าง ๆ ของร่างกายที่เกิดจากเชื้อซึ่งไวต่อยา ทั้งชนิดเฉียบพลันและเรื้อรังโดยเฉพาะการติดเชื้อ gram-negative bacilli เช่น *Acinetobacter baumannii* (รวมทั้ง *Acinetobacter baumannii* ที่ดื้อต่อยาต้านจุลชีพทุกชนาน), *Pseudomonas aeruginosa* (รวมทั้ง *Pseudomonas aeruginosa* ที่ดื้อต่อยาต้านจุลชีพทุกชนาน), *Escherichia coli* (รวมทั้ง ESBL-producing *Escherichia coli*), *Klebsiella pneumoniae* (รวมทั้ง ESBL-producing *Klebsiella pneumoniae*), *Enterobacter aerogenes, Citrobacter sp., Haemophilus influenza, Salmonella sp., Shigella sp., Proteus sp., Providencia sp., Serratia sp.* และบางสายพันธุ์ของ *Bordetella sp., Vibrio sp.* รวมทั้งรักษาการติดเชื้อ *Pseudomonas aeruginosa* ในทางเดินระบบหายใจในผู้ป่วย cystic fibrosis โดยการดูดพ่นผ่านหน้ากากพ่นยา (nebulization)

วิธีการใช้ยา :-
เมลลิสติน 150 มก. ชนิดฉีด สามารถให้ได้โดยวิธีฉีดเข้ากล้ามเนื้อ (IM) หรือฉีดเข้าหลอดเลือดดำ (IV) หรือหยดเข้าหลอดเลือดดำ (IV infusion) หรือดูดพ่นทางปาก (Oral inhalation)
ในการเตรียมยา ควรคำนึงถึงความเสี่ยงของการปนเปื้อนเชื้อโรค ดังนั้นควรใช้หลังจากการเตรียมยาโดยเร็วที่สุดและหากมียาเหลือจากการเปิดผสมแล้วไม่ควรเก็บไว้ใช้ต่อไป
ก่อนใช้ยาฉีดทุกครั้ง ควรพิจารณาดูว่ามีตะกอนหรือการเปลี่ยนสีของยาหรือไม่

การเตรียมยาสำหรับฉีดเข้ากล้ามเนื้อ (IM) และฉีดเข้าหลอดเลือดดำ (IV)
ละลายยา **เมลลิสติน 150 มก. ชนิดฉีด** ด้วยน้ำกลั่นสำหรับฉีดจำนวน 2 มิลลิลิตร ซึ่งจะได้ความเข้มข้นของยาประมาณ 75 มิลลิกรัม/มิลลิลิตร เขย่าให้ผงยาละลายโดยหมุนวนเบา ๆ ระวังอย่าให้เกิดฟอง
ควรให้ยาโดยการฉีดเข้าหลอดเลือดดำช้า ๆ ใช้เวลาฉีดนานกว่า 3-5 นาที ทุก 12 ชั่วโมง

การเตรียมยาสำหรับหยดเข้าหลอดเลือดดำ (IV infusion)
การฉีดการฉีดยาเข้าหลอดเลือดดำ (IV) อย่างช้า ๆ ใช้เวลาฉีดนานกว่า 3-5 นาที ทุก 12 ชั่วโมงในขนาดยาครึ่งหนึ่งของขนาดยาทั้งหมดต่อวันแล้วจึงนำขนาดยาที่เหลืออีกครึ่งหนึ่งมาผสมในสารละลายที่เข้ากันได้สำหรับหยดเข้าหลอดเลือดดำตัวใดตัวหนึ่ง ดังนี้ 0.9% sodium chloride injection, 5% dextrose , 5% dextrose และ 0.225% sodium chloride injection, 5% dextrose และ 0.45% sodium chloride injection, 5% dextrose และ 0.9% sodium chloride injection, lactated Ringer's solution หรือ 10% invert sugar เขย่าให้เข้ากันโดยหมุนวนเบา ๆ ระวังอย่าให้เกิดฟอง

การให้ยาสำหรับหยดเข้าหลอดเลือดดำ (IV infusion)
ควรให้หลังจากให้ยาขนาดเริ่มต้นโดยการฉีดเข้าหลอดเลือดดำ (IV) อย่างช้า ๆ ไปแล้ว 1-2 ชั่วโมง จากนั้นจึงให้ยาโดยการหยดเข้าหลอดเลือดดำโดยใช้เวลาหยดเข้าหลอดเลือดดำนานกว่า 22-23 ชั่วโมง อัตราในการหยดยาเข้าหลอดเลือดดำประมาณ 5-6 มก./ชั่วโมง ในผู้ป่วยไตปกติ และควรลดลงตามภาวะไตบกพร่อง

การเตรียมยาสำหรับดูดพ่นทางปาก (Oral inhalation)
สำหรับการดูดพ่นผ่านหน้ากากพ่นยา (nebulization) การเตรียมสารละลาย isotonic ทำได้โดยเจือจางกับสารละลาย 0.9% sodium chloride injection หรือ sterile water ที่เหมาะสมและไม่มีสารกันเสีย 2-4 มิลลิลิตร และควรใช้สารละลายทันทีหลังจากเจือจาง

ความคงตัว
แม้สารละลาย Colistin ในน้ำกลั่นสำหรับฉีดที่ความเข้มข้นประมาณ 75 มิลลิกรัม/มิลลิลิตร จะมีความคงตัวนาน 10 วัน เมื่อเก็บในตู้เย็น (2-8°C) หรือเก็บที่อุณหภูมิห้อง (25°C) หรือในสารละลาย 0.9% NSS หรือ D5W ที่ความเข้มข้นประมาณ 1.5 มิลลิกรัม/มิลลิลิตร จะมีความคงตัวนาน 72 ชั่วโมง เมื่อเก็บในตู้เย็น (2-8°C) หรือเก็บที่อุณหภูมิห้อง (25°C) **แต่อย่างไรก็ตามควรใช้น้ำยาหลังผสมที่เตรียมเสร็จใหม่ ๆ เท่านั้น**

ขนาดยาที่แนะนำ :-
ขนาดและวิธีการให้ยาขึ้นอยู่กับความรุนแรงของการติดเชื้อ สภาพผู้ป่วย การทำงานของไต และชนิดของเชื้อก่อโรคหรือใช้ตามแพทย์สั่ง
ขนาดยาที่แนะนำในผู้ป่วยไตปกติ คือ 2.5-5 มก./น้ำหนักตัว 1 กก./วัน (คิดปริมาณของยา Colistin) แบ่งให้วันละ 2-4 ครั้งขนาดเท่า ๆ กัน โดยวิธีฉีดเข้ากล้ามเนื้อ หรือฉีดเข้าหลอดเลือดดำ หรือหยดเข้าหลอดเลือดดำ (IV infusion)
ขนาดยาแนะนำต่อวันสูงสุด คือ 5 มก./น้ำหนักตัว 1 กก./วัน (คิดปริมาณของยา Colistin)
ขนาดยาที่ให้โดยการดูดพ่นผ่านหน้ากากพ่นยา (nebulization) เพื่อรักษาการติดเชื้อ *Pseudomonas aeruginosa* ในทางเดินระบบหายใจในผู้ป่วย cystic fibrosis ในผู้ใหญ่และเด็ก คือ 33.33-66.66 มก. วันละ 2-3 ครั้งต่อวัน

ขนาดยาในผู้ป่วยที่มีการทำงานของไตบกพร่อง
ควรมีการปรับลดขนาดการใช้ยาและหรือความถี่ในการให้ยาตามระดับความรุนแรงของไตที่บกพร่อง (พิจารณาค่า serum creatinine) ดังแสดงรายละเอียดในตาราง

ตารางแสดงขนาดยาในผู้ป่วยที่มีการทำงานของไตบกพร่อง

ระดับการทำงานของไต	ปกติ	บกพร่องเล็กน้อย	บกพร่องปานกลาง	บกพร่องรุนแรง
ค่า serum creatinine (mg/dL)	0.7-1.2	1.3-1.5	1.6-2.5	2.6-4
Urea clearance (% of normal)	80-100	40-70	25-40	10-25
ขนาดยาที่ใช้ (มก.)	100-150	75-115	66-150	100-150
ความถี่ของการให้ยาต่อวัน (ครั้ง)	2 ถึง 4	2	1 หรือ 2	ทุก 36 ชั่วโมง
ขนาดยาต่อวัน (มก.)	300	150-230	133-150	100
ขนาดยาที่ใช้ต่อวัน (มก./กก./วัน)	5	2.5-3.8	2.5	1.5

ข้อห้ามใช้ :-
ห้ามใช้ในผู้ป่วยที่มีประวัติแพ้ยานี้ หรือยากลุ่ม polymyxins

คำเตือนและข้อควรระวัง :-

คำเตือน :
1. ห้ามใช้ในผู้ที่แพ้ยานี้
2. ยานี้อาจทำให้เกิดอันตรายต่อไต และระบบประสาทได้

ข้อควรระวัง :
1. ขนาดยาสูงสุด : ไม่ควรเกิน 5 มก./น้ำหนักตัว 1 กก./วัน ในผู้ป่วยไตปกติ
2. ในการใช้ยา Colistimethate sodium ควรระวังการเกิดพิษต่อไต อาการที่อาจพบ ได้แก่ ปัสสาวะน้อยลง ค่า BUN และ creatinine เพิ่มขึ้น พบโปรตีนในปัสสาวะ ปัสสาวะเป็นเลือด ปัสสาวะมีสีคล้ำ หากพบอาการเหล่านี้ควรหยุดยาและควรมีการปรับลดขนาดยาให้เหมาะสม
3. ในการใช้ยา Colistimethate sodium ควรระวังการเกิดความผิดปกติ (ชั่วคราว) ของระบบประสาทได้ อาการที่อาจพบ ได้แก่ ชาไร้ความรู้สึกตามปลายมือปลายเท้า อาการเหน็บ อาการคล้ายมึนเมาได้ การพูดผิดปกติ เวียนศีรษะ วิงเวียน จุนงง กล้ามเนื้อทำงานไม่ประสานกัน ตาพร่า พูดไม่ชัด ซึ่งอาจพบได้ในช่วง 4 วันแรกของการรักษา และอาการควรหายไปหากหยุดยา ในกรณีพบความผิดปกติทางระบบประสาท ควรมีการเฝ้าระวังอย่างใกล้ชิด และควรมีการปรับลดขนาดยาให้เหมาะสม
4. เนื่องจากการใช้ยาต้านเชื้อแบคทีเรียรวมทั้ง Colistimethate sodium มีผลต่อแบคทีเรียปกติที่อยู่ในลำไส้และทำให้เกิดการเจริญเติบโตผิดปกติของเชื้อ clostridia ซึ่งพบว่า toxin ที่สร้างจาก Clostridium difficile เป็นสาเหตุของการเกิดลำไส้อักเสบชนิด pseudomembranous colitis ได้ ในผู้ป่วยที่ใช้ยานี้จึงควรมีการตรวจเฝ้าระวังอาการท้องเสีย ลำไส้อักเสบ รวมทั้ง pseudomembranous colitis อย่างใกล้ชิด กรณีเกิด pseudomembranous colitis ที่ไม่รุนแรง มักหายเองได้เมื่อหยุดยา กรณีมีอาการรุนแรงควรให้สารน้ำเกลือแร่และโปตัสเซียมแทนและให้การรักษาด้วยยาต้านเชื้อแบคทีเรียที่เหมาะสมต่อไป
5. ไม่ควรใช้ยานี้ร่วมกับยาที่มีพิษต่อไตและร่วมกับยากลุ่ม neuromuscular blockers เนื่องจากทำให้เพิ่มความเป็นพิษต่อไตและมีผลต่อระบบประสาทได้
6. การใช้ Colistimethate sodium โดยการสูดพ่นผ่านหน้ากากพ่นยา (nebulization) อาจเสี่ยงต่อการเกิดหลอดลมตีบ จึงควรอยู่ในดุลพินิจของแพทย์ การใช้ยากก่อนพ่นยา (premedication) ด้วยยาขยายหลอดลม อาจลดความรุนแรงของการเกิดหลอดลมตีบ

อันตรกิริยากับยาอื่น ๆ :-
1. การใช้ยานี้ร่วมกับยาที่มีพิษต่อไต เช่น ยากลุ่ม aminoglycosides, ยา amphotericin B, capreomycin, cephalothin, methoxyflurane, polymyxin B sulfate, vancomycin ทำให้เพิ่มความเป็นพิษต่อไตได้ จึงไม่ควรใช้ร่วมกัน
2. การใช้ยานี้ร่วมกับยากลุ่ม neuromuscular blockers เช่น tubocurarine, succinylcholine, ether, decamethonium, gallamine รวมทั้ง sodium citrate อาจทำให้เกิดอาการ neuromuscular blockade ได้ จึงควรใช้ด้วยความระมัดระวัง

การใช้ยาในสตรีมีครรภ์และสตรีระหว่างให้นมบุตร :-
ยังไม่มีข้อมูลความปลอดภัยอย่างเพียงพอของการใช้ยานี้ในสตรีมีครรภ์ จึงไม่ควรใช้ยานี้ในสตรีมีครรภ์เว้นแต่ประโยชน์ที่จะได้รับจะมีมากกว่าอันตรายอันอาจเกิดกับทารกในครรภ์อย่างชัดเจน
เนื่องจากไม่มีข้อมูลว่ายานี้ถูกขับออกทางน้ำนมหรือไม่ จึงไม่ควรใช้ยานี้ในสตรีที่เลี้ยงลูกด้วยน้ำนมตนเองหรือหากจำเป็นต้องใช้ยา ควรพิจารณางดการเลี้ยงลูกด้วยนมตนเองในระหว่างใช้ยา

อาการไม่พึงประสงค์ :-
อาการไม่พึงประสงค์ที่อาจพบ ได้แก่
ระบบไต : ปัสสาวะน้อยลง ค่า BUN และ creatinine เพิ่มขึ้น พบโปรตีนในปัสสาวะ ปัสสาวะเป็นเลือด ปัสสาวะมีสีคล้ำ ไตวาย
ระบบประสาท : ชาไร้ความรู้สึกตามปลายมือปลายเท้า อาการเหน็บ อาการคล้ายมึนเมาได้ การพูดผิดปกติ เวียนศีรษะ วิงเวียน จุนงง กล้ามเนื้อทำงานไม่ประสานกัน ตาพร่า พูดไม่ชัด
ระบบหายใจ : ภาวะหยุดหายใจชั่วคราว หยุดการหายใจ หลอดลมตีบ หายใจอึดอัด
อื่น ๆ : ผื่น ลมพิษ คัน มีไข้ ก้างเส้นใจ ปวดบริเวณที่ฉีด นอกจากนี้อาจพบความผิดปกติของเม็ดเลือด (พบน้อย) เช่น leucopenia, granulocytopenia เป็นต้น

การได้รับยาเกินขนาดและวิธีการรักษา :-
การมีได้รับยาเกินขนาดทำให้เกิด neuromuscular blockade ได้แก่ ชาไร้ความรู้สึก เมื่อยชา สับสน เวียนศีรษะ กล้ามเนื้อทำงานไม่ประสานกัน อาการคางทะคุก การพูดผิดปกติ ภาวะหยุดหายใจชั่วคราว กล้ามเนื้อควบคุมการหายใจเป็นอัมพาต หยุดการหายใจ และอันตรายถึงชีวิต นอกจากนี้ยังอาจทำให้ไตวายได้ อาการที่พบได้แก่ ปัสสาวะน้อยลง ค่า BUN และ creatinine เพิ่มขึ้น
การรักษากรณีได้รับยาเกินขนาด : ควรหยุดให้ยาทันทีและให้การรักษาตามอาการ
Colistimethate sodium สามารถขจัดออกจากร่างกายโดยวิธี hemodialysis และมีบางส่วนสามารถขจัดออกจากร่างกายโดยวิธี peritoneal dialysis

สภาวะการเก็บรักษา :-
เก็บให้พ้นมือเด็ก
ควรเก็บยาผงแห้งก่อนผสมที่อุณหภูมิต่ำกว่า 30°C
ไม่ควรเก็บสารละลายโดยการแช่แข็ง

รูปแบบยาและขนาดบรรจุที่มีการจำหน่าย :-
ผงยาปราศจากเชื้อ สำหรับละลายเพื่อใช้ฉีด บรรจุในขวดแก้วใส ไม่มีสี (glass type III) จุกยาง (chlorobutyl) สีเทา ฝาอะลูมิเนียม แต่ละขวดบรรจุผงยาเทียบเท่า Colistin 150 มิลลิกรัม มีทั้งชนิดบรรจุกล่องเดี่ยวและไม่บรรจุกล่องเดี่ยว กล่องละ 1, 5, 10, 20, 30, 50 และ 100 ขวด

วันที่มีการแก้ไขปรับปรุงเอกสาร (13/11/2017)

ผู้ผลิต :-
บริษัท สยามเภสัช จำกัด
123 ซอยโชคชัยร่วมมิตร ถนนโกวิทสีรังสิต แขวงจอมพล เขตจตุจักร กรุงเทพมหานคร 10900 ประเทศไทย
และเลขที่ 9 ซอยโชคชัยร่วมมิตร 3 ถนนโกวิทสีรังสิต แขวงดินแดง เขตดินแดง กรุงเทพมหานคร 10400 ประเทศไทย
ผู้แทนจำหน่าย :-
บริษัท สยามฟาร์มาซูติคอล จำกัด
171/1-2 ซอยโชคชัยร่วมมิตร ถนนโกวิทสีรังสิต แขวงจอมพล เขตจตุจักร กรุงเทพมหานคร 10900 ประเทศไทย
โทร. 02-6259999

Colistin-150
FOR IV / IM

Composition :
Each vial contains :- Sterile Colistimethate Sodium equivalent to Colistin 150 mg

Product description :
White or yellowish white sterile powder to be dissolved in sterile solution for injection.

Pharmacodynamic :
Colistimethate Sodium is hydrolyzed in aqueous solution and body fluids to Colistin which has bactericidal action to susceptible organisms. It acts primarily by binding to membrane phospholipids and disrupting the bacterial cytoplasmic membrane. It is particularly effective against *Pseudomonas aeruginosa*. Colistimethate Sodium has a bactericidal action on most gram-negative bacilli and of the other gram-negative organisms, *Acinetobacter* spp., *Escherichia coli*, *Enterobacter* spp., *Klebsella* spp., *Haemophilus influenzae*, *Bordetella pertussis*, *Salmonella* spp. and *Shigella* spp. are sensitive.

Pharmacokinetics :
Peak plasma concentrations usually occur 2 to 3 hours after an intramuscular injection of colistimethate sodium. Plasma protein binding of colistimethate sodium is low. The serum half-life of colistimethate sodium is 2 to 3 hours but is prolonged in renal impairment (values of 10 to 20 hours have been reported in patients with a creatinine clearance of less than 20 mL/minute). Colistimethate is mainly excreted by glomerular filtration as changed and unchanged drug and up to 80% of a parenteral dose may be recovered in the urine within 24 hours. Excretion is more rapid in children than in adults. Colistin crosses the placenta. It is distributed into breast milk.

Indication :
COLISTIN-150 has been used in the treatment of severe gram-negative infections, especially those due to *Pseudomonas aeruginosa* and in multidrug-resistant *Pseudomonas* or *Acinetobacter* CNS infections.

Recommended dose :
Each mg of colistin base has a potency of 30,000 I.U. and each mg of colistimethate sodium has a potency of 12,500 I.U.

Parenteral dosage
The usual IM or IV dosage of colistimethate sodium for adults and children with normal renal function is 2.5-5 mg/kg of colistin daily given in 2-4 divided doses, depending on the severity of the infection.
The maximum IM or IV dosage of colistimethate sodium for patients with normal renal function is 5 mg/kg of colistin daily.

Oral inhalation dosage
Colistimethate sodium has been given by oral inhalation by nebulization in a dosage of 33.33 – 66.66 mg (1-2 million I.U.) of colistin 2 or 3 times daily.

Administration in renal impairment
The dose and frequency of IM or IV colistimethate sodium should be decreased in proportion to the degree of renal impairment.
- Serum creatinine 1.3 to 1.5 mg/100 mL : 2.5-3.8 mg/kg daily given IM or IV in 2 divided doses.
- Serum creatinine 1.6 to 2.5 mg/100 mL : 2.5 mg/kg daily given IM or IV in a single dose or in 2 divided doses.
- Serum creatinine 2.6 to 4.0 mg/100 mL : 1.5 mg/kg daily given IM or IV every 36 hours.

Mode of administration :
COLISTIN-150 is administered by IM injection, IV injection, or continuous IV infusion. The drug also has been administered by oral inhalation via nebulization.
Parenteral administration : COLISTIN-150 is reconstituted by adding 2 mL of sterile water for injection to a vial, swirled gently. The resultant solution contains 75 mg of colistin per mL.
- IV injection : For direct intermittent IV administration, one-half of the total daily dose should be injected directly into a vein over a 3- to 5- minute period every 12 hours.
- IV infusion : For continuous IV infusion, one-half of the total daily dose should be injected directly into a vein over a 3- to 5- minute period; the remaining one-half of the total daily dose should be added to a compatible IV solution (0.9% NaCl, 5% dextrose, 5% dextrose and 0.225%, 0.45% or 0.9% NaCl, lactate Ringer 's, or 10% invert sugar) and administered 1-2 hours later (over the next 22-23 hours) by slow IV infusion. The infusion rate should be 5-6 mg/hour in patients with normal renal function. For patients with impaired renal function, the infusion rate should be reduced depending on the degree of renal impairment.
The specific IV solution and volume of the solution used should be based on the patients' fluid and electrolyte requirements.
- IM administration : For IM injection, the appropriate dose of reconstituted solution should be given IM.
Stability of reconstituted solution : Following reconstitution with sterile water for injection,COLISTIN-150 solutions contain 75 mg of colistin per mL and should be stored at 2-8 °C or 25 °C and used within 7 days. However, reconstituted solutions should be used freshly prepared.
Oral Inhalation : For oral inhalation via nebulization, an isotonic solution of COLISTIN-150 has been prepared by diluting the appropriate dose in 2-4 mL of preservative-free 0.9% sodium chloride injection, sterile water, or a mixture of 0.9% sodium chloride injection and sterile water. The solution should be used promptly after prepared.

Contraindication :
1. Hypersensitivity to colistimethate sodium.
2. Patients who have myasthenia gravis.

Precaution :
- Neurotoxic reactions such as dizziness, confusion, and visual disturbances can occur during parenteral therapy and patients so affected should not drive or operate machinery.
- Plasma-concentration monitoring during systemic treatment is recommended in neonates, patient with renal impairment, and those with cystic fibrosis. Peak plasma-colistin concentrations of 10 to 15 mg/litre are recommended.
- Premixing of colistimethate in an aqueous solution and stc it for longer than 24 hours results in increased concentrations of co in solution and increases the potential for lung toxicity. Therefore, sh be given promptly after preparation.
- Colistin has been associated with acute attacks of porph and is considered unsafe in porphyric patients.

Interactions with other medicaments :
- Use with cephalosporins group, vancomycin, capreom minocycline, amphotericin B, bacitracin, cisplatin, methoxyflu polymyxin B may result in additive side effect of neurotoxic, oto and nephrotoxic.
- If use before, during or after surgical procedures in whic neuromuscular blocking agent is administered, the possibility of longed duration of neuromuscular blockade (or recurarization, pa larly postoperatively) should be considered.

Pregnancy and lactation :
Pregnancy : Avoid. Possible risk of fetal toxicity especial second and third trimesters.
Lactation : Avoid. It is distributed into breast milk.

Undesirable effects :
- Dizziness, confusion and visual disturbances.
- Pain and local irritation are reported to be less troubles after intramuscular injection.
- Neurotoxicity reported especially with excessive doses (ding apnoea, perioral and peripheral paraesthesia, vertigo; ra vasomotor instability, slurred speech, confusion, psychosis, vi disturbances); nephrotoxicity; hypersensitivity reactions including injection-site reactions.

Overdose and Treatment :
Overdosage may cause apnoea, muscle weakness, ver slurred speech, vasomotor instability, visual disturbances, confu psychosis and renal insufficiency.
Treatment of overdose
No antidote is available. Management of overdose is by me of supportive treatment and measures designed to increase clear of colistimethate sodium such as inducing an osmotic diuresis mannitol, peritoneal dialysis or prolonged haemodialysis.

Storage condition :
Store below 30 °C

Dosage forms and packaging available :
Clear colorless glass vial with flip-off cap contains ste colistimethate sodium equivalent to colistin 150 mg packed or unpa in paper box of 1, 2, 3, 4, 5, 10, 12, 24, 50 and 100 vials.

Manufactured by : **MILLIMED CO., LTD.** Samut Prakan, Thail

Distributed by : **UNIVERSAL MEDICAL INDUSTRY CO.,LTD.**
9/425-7 Ram-Indra Road, Anusaowaree,
Bangkhen, Bangkok 10220 Thailand.
Tel : (662) 971-5468 Fax : (662) 971-5470

Date of revision of package insert : 25.11.16

โคลิสติน-150
FOR IV / IM

ส่วนประกอบ :
ใน 1 vial ประกอบด้วย Sterile Colistimethate Sodium เทียบเท่ากับ Colistin 150 มก.

ลักษณะของผลิตภัณฑ์ :
ผงยาปราศจากเชื้อสีขาวถึงขาวออกเหลือง สำหรับละลายในตัวทำละลายเพื่อใช้ฉีด

เภสัชพลศาสตร์ :
เมื่อยา Colistimethate sodium เข้าสู่ร่างกาย จะถูก Hydrolyzed ได้ตัวยา Colistin ซึ่งมีฤทธิ์ในการฆ่าเชื้อแบคทีเรียที่ไวต่อยานี้ โดยจะจับกับ phospholipid ที่ membrane ของแบคทีเรีย ซึ่งจะทำให้เยื่อหุ้มเซลล์ของแบคทีเรียเสียหาย ยามีประสิทธิผลดีกับ *Pseudomonas aeruginosa*, แบคทีเรียแกรมลบกลุ่ม bacilli รวมถึงแบคทีเรียแกรมลบกลุ่มอื่นๆ ได้แก่ *Acinetobacter* spp., *Escherichia coli*, *Enterobacter* spp., *Klebsella* spp., *Haemophilus influenzae*, *Bordetella pertussis*, *Salmonella* spp. และ *Shigella* spp.

เภสัชจลนศาสตร์ :
เมื่อให้ยา Colistimethate sodium โดยการฉีดเข้ากล้ามเนื้อ ระดับความเข้มข้นสูงสุดของยาในพลาสมาจะอยู่ที่ประมาณ 2 - 3 ชั่วโมง ยาจับกับโปรตีนพลาสมาได้ต่ำ มีค่าครึ่งชีวิตประมาณ 2 - 3 ชั่วโมง แต่จะนานขึ้นในผู้ป่วยที่มีสภาวะไตบกพร่อง (ประมาณ 10 - 20 ชั่วโมง ในกรณีที่มีค่า creatinine clearance น้อยกว่า 20 มล./นาที) ยาถูกขับออกโดยผ่านการกรองที่ไตเป็นส่วนใหญ่ ทั้งในรูปที่เปลี่ยนแปลงและไม่เปลี่ยนแปลง โดยพบว่าประมาณ 80% ของปริมาณยาที่ผ่านทางหลอดเลือดดำจะถูกกำจัดออกทางปัสสาวะภายใน 24 ชั่วโมง การขจัดยาในเด็กจะเร็วกว่าในผู้ใหญ่ นอกจากนี้ Colistin ยังสามารถแพร่กระจายผ่านรกและน้ำนมได้

ข้อบ่งใช้ :
สำหรับรักษาโรคติดเชื้อแบคทีเรียแกรมลบที่รุนแรง โดยเฉพาะที่เกิดจากเชื้อ *Pseudomonas aeruginosa* นอกจากนี้ยังใช้ในการรักษาการติดเชื้อของระบบประสาทส่วนกลางชนิด multidrug-resistant *Pseudomonas* หรือ *Acinetobacter*

ขนาดยาที่แนะนำ :
ด้วยยาสำคัญ Colistin 1 มิลลิกรัม มีความแรงเท่ากับ 30,000 หน่วยสากล และด้วยยาสำคัญในรูป Colistimethate sodium 1 มิลลิกรัมจะมีความแรงเท่ากับ 12,500 หน่วยสากล

ขนาดยาสำหรับให้โดยการฉีด
ขนาดยาสำหรับการฉีดเข้ากล้ามเนื้อและการฉีดเข้าหลอดเลือดดำสำหรับผู้ใหญ่และเด็กที่มีการทำงานของไตปกติ คือ 2.5 - 5 มก./กก./วัน ของยาในรูป Colistin แบ่งให้วันละ 2 - 4 ครั้ง ขึ้นกับความรุนแรงของการติดเชื้อ
ขนาดยาสูงสุดสำหรับการฉีดเข้ากล้ามเนื้อและการฉีดเข้าหลอดเลือดดำสำหรับผู้ใหญ่และเด็กที่มีการทำงานของไตปกติ คือ 5 มก./กก./วัน ของยาในรูป Colistin
ขนาดยาสำหรับให้โดยการสูดพ่นเข้าทางปาก
ขนาดยา Colistimethate sodium สำหรับให้ทางการสูดพ่นเข้าทางปากโดยผ่านเครื่อง Nebulizer คือ 33.33 - 66.66 มิลลิกรัม (1 - 2 ล้านหน่วยสากล) ของยาในรูป Colistin โดยให้ยา 2 - 3 ครั้งต่อวัน

การใช้ยาในผู้ป่วยที่มีการทำงานของไตบกพร่อง
ขนาดยาและความถี่ของการให้ยาทางการฉีดเข้ากล้ามเนื้อหรือฉีดเข้าหลอดเลือดดำควรลดลงตามระดับการทำงานของไตที่บกพร่อง
- ค่าครีอะตินินในซีรัม 1.3 - 1.5 มก. ต่อ 100 มล. : 2.5 - 3.8 มก./กก./วัน ฉีดเข้ากล้ามเนื้อและการฉีดเข้าหลอดเลือดดำ โดยแบ่งให้ยาวันละ 2 ครั้ง
- ค่าครีอะตินินในซีรัม 1.6 - 2.5 มก. ต่อ 100 มล. : 2.5 มก./กก./วัน ฉีดเข้ากล้ามเนื้อและการฉีดเข้าหลอดเลือดดำ โดยให้ยาภายในครั้งเดียว หรือแบ่งเป็นวันละ 2 ครั้ง
- ค่าครีอะตินินในซีรัม 2.6 - 4.0 มก. ต่อ 100 มล. : 1.5 มก./กก./วัน ฉีดเข้ากล้ามเนื้อและการฉีดเข้าหลอดเลือดดำ ทุก 36 ชั่วโมง

วิธีการใช้ยา :
โคลิสติน-150 สามารถบริหารยาผ่านการฉีดเข้ากล้ามเนื้อ, ฉีดหรือหยดเข้าหลอดเลือดดำ และสามารถให้โดยการสูดพ่นทางปากผ่านเครื่อง Nebulizer ได้

การให้ยาโดยการฉีด
ผสมยาโคลิสติน-150 โดยการเติมน้ำกลั่นปราศจากเชื้อปริมาณ 2 มิลลิลิตรลงไปในขวดยาฉีด เขย่าสารละลายเบาๆ สารละลายที่ได้จะมียา Colistin 75 มก./มล.
- **การฉีดเข้าหลอดเลือดดำ**: สำหรับการฉีดเข้าหลอดเลือดดำแบบไม่ต่อเนื่อง ให้ยาครึ่งหนึ่งของขนาดยาต่อวันทั้งหมด โดยฉีดเข้าหลอดเลือดดำโดยตรง นาน 3 - 5 นาที ทุก 12 ชั่วโมง
- **การหยดเข้าหลอดเลือดดำ**: สำหรับการหยดเข้าหลอดเลือดดำแบบต่อเนื่อง ให้ยาครึ่งหนึ่งของขนาดยาต่อวันทั้งหมด โดยฉีดเข้าหลอดเลือดดำโดยตรง นาน 3 - 5 นาที ยาอีกครึ่งหนึ่งของขนาดยาต่อวันที่เหลืออยู่ ควรผสมกับสารละลายสำหรับฉีดเข้าหลอดเลือดดำที่เข้ากัน (0.9% NaCl, 5% dextrose, 5% dextrose ที่ผสมกับ 0.225% หรือ 0.45% หรือ 0.9% NaCl, Lactate Ringer 's, 10% invert sugar) แล้วเริ่มให้ยาหลังการฉีดยาครึ่งแรกเข้าหลอดเลือดดำโดยตรงไปแล้ว 1 - 2 ชั่วโมง โดยหยดยาเข้าหลอดเลือดดำ (IV infusion) อย่างช้าๆ นาน 22 - 23 ชั่วโมง ในผู้ป่วยที่มีการทำงานของไตปกติ อัตราการหยดยาเข้าหลอดเลือดดำควรเป็น 5 - 6 มก./ชม. และในผู้ป่วยที่มีการทำงานของไตบกพร่อง อัตราการหยดยาเข้าหลอดเลือดดำควรลดลงตามระดับการทำงานของไตที่บกพร่อง
ชนิดและปริมาณของสารละลายยาฉีดที่ใช้ ควรเป็นไปตามความต้องการสารน้ำและอิเล็กโตรไลต์ของผู้ป่วย
- **การฉีดเข้ากล้ามเนื้อ**: สำหรับการฉีดยาเข้ากล้ามเนื้อ ขนาดยาของสารละลายฉีดที่ใช้ควรมีความเหมาะสม
ความคงตัว: สารละลายยาฉีดโคลิสติน-150 ในน้ำกลั่นสำหรับฉีดที่มีความเข้มข้น 75 มก./มล. หากเก็บไว้ในตู้เย็น (2 - 8 °C) หรืออุณหภูมิห้อง (25 °C) สามารถมีความคงตัวนาน 7 วัน แต่อย่างไรก็ตามควรใช้ยาผสมที่เตรียมเสร็จใหม่ๆ เท่านั้น

การสูดพ่นทางปาก
สำหรับวิธีการสูดพ่นทางปากโดยผ่านเครื่อง Nebulizer เตรียมสารละลาย isotonic ของยาโดยละลายยาในขนาดที่เหมาะสมในน้ำเกลือปราศจากเชื้อและปราศจากสารกันเสีย 0.9% NaCl น้ำกลั่นปราศจากเชื้อ หรือสารละลายผสมของน้ำเกลือปราศจากเชื้อ 0.9% NaCl กับน้ำกลั่นปราศจากเชื้อปริมาณ 2 - 4 มิลลิลิตร ควรใช้สารละลายยาทันทีหลังจากผสม

ข้อห้ามใช้ :
1. ห้ามใช้ในผู้ที่แพ้ยานี้
2. ผู้ที่มีอาการของโรค Myasthenia gravis

ข้อควรระวัง :
- ยามีพิษต่อระบบประสาท ทำให้เกิดอาการวิงเวียน สับสน และการมองเห็นผิดปกติ ดังนั้นจึงไม่ควรขับรถหรือทำงานเกี่ยวกับเครื่องจักร
- ควรมีการติดตามระดับความเข้มข้นของยาในพลาสมาระหว่างการรักษาด้ ขนาดยาปกติในทารกแรกเกิด ผู้ป่วยที่มีสภาวะไตบกพร่องและผู้ที่มีภาวะ cystic fibr sis โดยความเข้มข้นของ Colistin ในพลาสมาที่แนะนำควรอยู่ในช่วง 10 - 15 มก./ล
- ควรใช้หลังการเตรียมทันที เนื่องจากถ้าผสมยาไว้นานกว่า 24 ชั่วโมง จะท ให้ระดับความเข้มข้นของ Colistin เพิ่มขึ้นและเป็นพิษต่อปอดได้
- เนื่องจาก Colistin อาจทำให้เกิดอาการ porphyria แบบเฉียบพลัน ดัง จึงควรพิจารณาความปลอดภัยการใช้ยานี้ในผู้ป่วยที่เป็นโรค porphyria

อันตรกิริยากับยาอื่นๆ :
- การใช้ร่วมกับยา cephalosporin, vancomycin, capreomycin, min cycline, amphotericin B, bacitracin, cisplatin, methoxyflurane และ po myxin B อาจทำให้เพิ่มความเป็นพิษต่อระบบสมอง, ไต และไตได้
- การใช้ยาร่วมกับยากลุ่ม Neuromuscular blocking ก่อน ระหว่างหรือ การผ่าตัด อาจมีผลทำให้ฤทธิ์ Neuromuscular blockade (หรือ recurarization เฉพาะอย่างยิ่งหลังผ่าตัด) นานขึ้นได้

สตรีมีครรภ์และสตรีให้นมบุตร :
สตรีมีครรภ์ : ไม่ควรใช้ เนื่องจากมีความเสี่ยงที่จะเป็นอันตรายต่อทารกในค โดยเฉพาะการตั้งครรภ์ในช่วงไตรมาสที่สองและสาม
สตรีให้นมบุตร : ยาสามารถผ่านน้ำนมได้ ดังนั้นจึงควรหลีกเลี่ยงการใช้ยา ระหว่างเลี้ยงลูกด้วยน้ำนมตนเอง

อาการไม่พึงประสงค์ :
- ทำให้เกิดอาการวิงเวียน สับสน และการรบกวนการมองเห็น
- อาจทำให้เกิดอาการปวดและระคายเคืองบริเวณฉีดได้บ้าง ภายหลังการฉีดเข้ากล้าม
- มีรายงานความเป็นพิษต่อระบบประสาท โดยเฉพาะเมื่อมีการใช้ยาเกินข (อาการที่เกิดขึ้น ได้แก่ หยุดหายใจ เยื่อบริเวณรอบปากและปลายมือปลายเท้า ทร ลำบาก การควบคุมกล้ามเนื้อผิดปกติ พูดไม่ชัด สับสน อาการทางจิต การมองเห็นผ ปกติ) ภาวะพิษต่อระบบไต ภาวะไวเกินต่อยา ได้แก่ ผื่นแดง ระคายเคืองบริเวณที่ฉีด

การได้รับยาเกินขนาดและวิธีการรักษา :
การได้รับยาเกินขนาดอาจก่อให้เกิดอาการหยุดหายใจชั่วขณะ กล้ามเนื้ออ่อนแรง วิงเวียน คำพูดเละเลือน ระบบประสาทควบคุมกล้ามเนื้อผิดปกติ การมองเห็นผิดปกติ สับสน และเกิดพิษต่อไต

วิธีการรักษา
ให้การรักษาตามอาการที่เกิด และอาจเพิ่มการรักษาโดยการทำ osmot diuresis ด้วย mannitol, peritoneal dialysis หรือ prolonged haemodialys

สภาวะการเก็บรักษา :
เก็บยาที่อุณหภูมิต่ำกว่า 30 องศาเซลเซียส

รูปแบบยาและขนาดบรรจุที่มีจำหน่าย :
ขวดแก้วใสชนิด vial มีปิดด้วยฝา flip-off แต่ละขวดบรรจุ Sterile Colistin thate Sodium เทียบเท่ากับ Colistin 150 มก. และบรรจุหรือไม่บรรจุในกล่องกระ ละ 1, 2, 3, 4, 5, 10, 12, 24, 50 และ 100 ขวด

ผลิตโดย : **บริษัท มิลลิเมด จำกัด**
สมุทรปราการ ประเทศไทย

จัดจำหน่ายโดย : **บริษัท ยูนิเวอร์แซล เมดิคอล อินดัสตรี จำกัด**
9/425-7 ถ.รามอินทรา แขวงอนุสาวรีย์ เขตบางเขน กทม. 10220
โทร : (662) 971-5468 โทรสาร : (662) 971-5470

วันที่มีการแก้ไขปรับปรุงเอกสาร : 25.11.16

Appendix C: Validation of LC-MS/MS method for colistin determination

Principle of method validation

Linearity, standard calibration curve, and LLOQ

Linearity was tested using a set of calibration points, prepared in blank human plasma covering a range of interests. The calibration curve was established by plotting the peak area ratio (y) versus the nominal concentration (x) of the analyte. The calibration curves were derived by weighted (1/y) linear regression analysis. The correlation coefficient (r^2) of at least 0.99 was set as a criterion of acceptance. The lower limit of quantification (LLOQ) was assessed as the lowest concentration on the calibration curve that produced a signal/noise ratio of 5 and established based on 6 replications during 5 consecutive days. The acceptable accuracy and precision of LLOQ were within ±20%.

Accuracy and precision

Intra- and inter-day accuracy and precision were analyzed using 5 replicates at three levels of QC samples (LQC, MQC, and HQC). Intra- and inter-day accuracy were expressed as percentages of theoretical concentration at each QC level (85-115%. Intra- and inter-day precision were evaluated as the coefficient of variation (%CV) within 15%.

Specificity

Specificity was carried out by screening 6 different batches of blank human plasma. Each batch was tested for interference from endogenous plasma components by comparing the chromatograms of blank plasma with that of the corresponding spiked plasma at LLOQ concentration. The acceptance criterion was defined as no other peak observed at the same retention time of analytes and internal standard (IS) (netilmicin).

Matrix effect and carryover effect

Matrix effect was assessed by the signal from endogenous molecules of blank plasma that interfered with the signal from analytes. Six individual blank plasma were prepared at two different concentrations (low and high). The matrix effect was assessed by comparing the peak areas of analytes with blank plasma spiked with analytes after

extraction to those of the analytes from neat solution at equivalent concentration and reported as matrix factor. For carryover effect, three blank samples were injected following the highest calibrator (upper limit of quantification, ULOQ).

Results of method validation

Linearity and LLOQ

Seven points plasma calibration curves for formed colistin were created by plotting the peak area ratio of (colistin A + colistin B) to IS against a nominal concentration of calibrators. Weighted (1/y) linear regression analysis exhibited good linearity and reproducibility with r^2 values > 0.99 in all experiments. The linearity regression of the peak area ratio versus concentrations was fitted over the concentration range of 0.1-6.4 mg/L. The LLOQ value was 0.1 mg/L. The example of calibration curve is shown in Figure AC1.

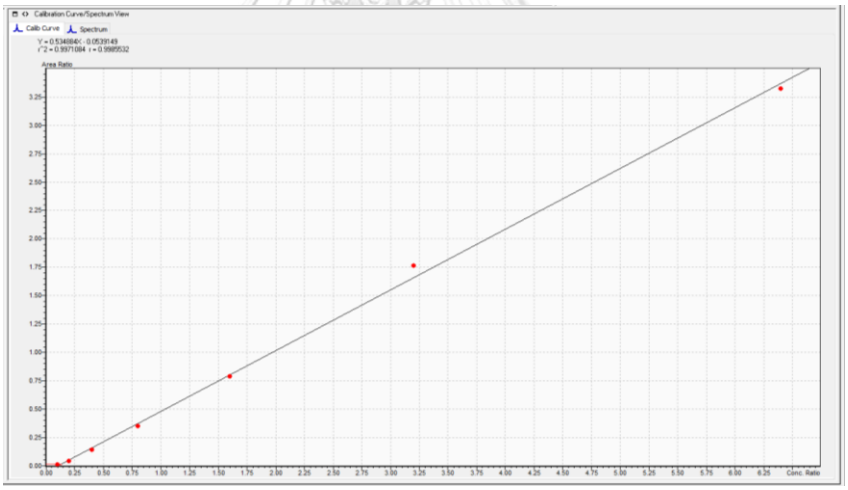


Figure AD1. Example of colistin calibration curve range.

Accuracy and precision

The accuracy and precision results were summarized in Table AC1. The results are all within the acceptable range of variation and deviation recommended by the FDA guidance (<15%), demonstrating that this method is reproducible.

TABLE AC1. Intra- and inter-day accuracy and precision for colistin QC samples.

Colistin levels	Intra-day		Inter-day	
	Precision (%CV)	**Accuracy (%nominal)**	**Precision (%CV)**	**Accuracy (%nominal)**
Low QC (0.3 mg/L)	9.36	99.89	3.08	99.89
Medium QC (0.6 mg/L)	9.89	98.46	2.69	98.46
High QC (1.2 mg/L)	5.27	101.20	6.24	101.57
LLOQ (0.1 mg/L)	3.94	102.33	5.59	103.33

Specificity

No other interfering peak was observed at the same retention time of the analytes and IS in all six different batches of blank plasma. Six batches of plasma were pooled and used to prepare a blank, calibrators, and QC samples for the entire experiment.

Matrix effect

The matrix factor (mean ± SD) at LQC and HQC levels were found to be 1.07 ± 0.05 and 1.06 ± 0.02 for formed colistin. This method demonstrated a minimal matrix effect on the ionization of formed colistin.

Carryover

The percentage of carryover was < 0.2% and the detected concentration in the blank sample was less than the LLOQ concentration of all analytes.

Appendix D: Ethical approvals

COA No. 256/2018
IRB No. 042/61

INSTITUTIONAL REVIEW BOARD
Faculty of Medicine, Chulalongkorn University
1873 Rama 4 Road, Patumwan, Bangkok 10330, Thailand, Tel 662-256-4493

Certificate of Approval

The Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, has approved the following study in compliance with the International guidelines for human research protection as Declaration of Helsinki, The Belmont Report, CIOMS Guideline and International Conference on Harmonization in Good Clinical Practice (ICH-GCP)

Study Title : Population Pharmacokinetics of Intravenous Colistin in Pediatrics (POPPICOP study)

Study Code : -

Principal Investigator : Noppadol Wacharachaisurapol, M.D., BSc.

Affiliation of PI : Ph.D. in Clinical Sciences (International Program), Graduate Affairs, Faculty of Medicine, Chulalongkorn University.

Review Method : Full board

Continuing Report : At least once annually or submit the final report if finished.

Document Reviewed :

1. Doctoral Dissertation Proposal version 1.1 dated 27 February 2018
2. Protocol Synopsis version 1.1 dated 27 February 2018
3. Information sheet for the legal representative/guardian of the Participant in the Research Program version 1.1 dated 27 February 2018
4. Informed consent to participant the legal representative/guardian version 1.1 dated 27 February 2018

Approval granted is subject to the following conditions: (see back of this Certificate)

5. Information sheet for research participant ages 7-12 years version 1.1 dated 27 February 2018
6. Informed consent for participating volunteers ages 7-12 years version 1.1 dated 27 February 2018
7. CRF Enrollment Day 1 Version 1.1 date 27 February 2018
8. Blood Sampling CRF Version 1.1 date 27 February 2018
9. Microbiological data Version 1.1 date 27 February 2018
10. Curriculum Vitae and GCP Training
    - Noppadol Wacharachaisurapol, M.D., BSc.
    - Assoc.Prof. Thanyawee Puthanakit, M.D.
    - Asst.Prof. Thitima Wattanavijitkul, M.D.

Signature ..... Signature .....

(Emeritus Professor Tada Sueblinvong MD)
Chairperson
The Institutional Review Board

(Assistant Professor Prapapan Rajatapiti MD, PhD)
Member and Secretary
The Institutional Review Board

Date of Approval : March 15, 2018
Approval Expire Date : March 14, 2019

Approval granted is subject to the following conditions: (see back of this Certificate)

REC-QSNICH.36T

คณะกรรมการจริยธรรมการวิจัยในมนุษย์
สถาบันสุขภาพเด็กแห่งชาติมหาราชินี

4 มกราคม 2562

โครงการวิจัยเรื่อง : การศึกษาเภสัชจลศาสตร์ประชากรของยาโคลิสตินชนิดฉีดเข้าหลอดเลือดดำในผู้ป่วยเด็ก
(Population pharmacokinetics of intravenous colistin in pediatrics (POPPICOP study))
ผู้ดำเนินการวิจัย : นายแพทย์นพดล วัชระชัยสุรพล
ผู้ร่วมวิจัยในสถาบันฯ : รศ. ดร. แพทย์หญิงวารุณี พรรณพานิช วานเดอพิทท์
สถานที่ดำเนินการวิจัย : สถาบันสุขภาพเด็กแห่งชาติมหาราชินี
ระยะเวลาดำเนินการ : 1 ตุลาคม 2561 30 พฤศจิกายน 2562
เอกสารที่พิจารณา :

1. ประวัติคณะผู้วิจัย
2. แบบฟอร์ม Biological Material Transfer Agreement

เอกสารที่รับรอง :

1. แบบเสนอโครงการวิจัยเพื่อขอรับการพิจารณาจากคณะกรรมการจริยธรรมการวิจัยในมนุษย์สถาบันสุขภาพเด็กแห่งชาติมหาราชินี (REC-QSNICH.03) (Version 2 Date 27 พฤศจิกายน 2561 : ฉบับภาษาไทย)
2. คำอธิบายสำหรับผู้เข้าร่วมในโครงการวิจัย (Information Sheet for Research Participant) (REC-QSNICH.05) (Version 2 Date 27 พฤศจิกายน 2561)
3. คำอธิบายสำหรับผู้เข้าร่วมในโครงการวิจัยสำหรับอาสาสมัครเด็กอายุ 7-12 ปี (Information Sheet for Research Participant) (REC QSNICH.06) (Version 2 Date 27 พฤศจิกายน 2561)
4. หนังสือแสดงความยินยอมเข้าร่วมโครงการวิจัยสำหรับผู้แทนโดยชอบธรรม/ผู้ปกครอง (Informed Consent Form) (REC QSNICH.08) (Version 2 Date 27 พฤศจิกายน 2561)
5. หนังสือแสดงความยินยอมเข้าร่วมโครงการวิจัยสำหรับอาสาสมัครเด็กอายุ 7 12 ปี (Informed Assent Form) (REC-QSNICH.09) (Version 2 Date 27 พฤศจิกายน 2561)
6. CRF-Enrollment Day 1-POPPICOP STUDY (Version 2 Date 27 พฤศจิกายน 2561)
7. CRF-Blood Sampling Worksheet-POPPICOP STUDY (Version 2 Date 27 พฤศจิกายน 2561)

คณะกรรมการจริยธรรมการวิจัยในมนุษย์ สถาบันสุขภาพเด็กแห่งชาติมหาราชินี ได้พิจารณารับรองโครงการวิจัยโดยยึดหลักเกณฑ์ตามคำประกาศเฮลซิงกิ (Declaration of Helsinki) และแนวทางการปฏิบัติการวิจัยทางคลินิกที่ดี (ICH GCP) ทั้งนี้ให้ดำเนินการวิจัยตามเอกสารฉบับภาษาไทยเท่านั้น โดยขอให้รายงานความก้าวหน้าทุก 12 เดือน

(แพทย์หญิงรัตโนทัย พลับรู้การ)
ประธานคณะกรรมการจริยธรรมการวิจัยในมนุษย์
สถาบันสุขภาพเด็กแห่งชาติมหาราชินี

เลขที่ : REC.038/2562 (Full Board)
รหัสโครงการ : Document No.61 077
เลขที่เอกสารรับรอง : REC.038/2562

รับรองตั้งแต่วันที่ 3 ธันวาคม 2561 ถึงวันที่ 2 ธันวาคม 2562
ประชุมครั้งที่ 12/2561 วันที่ 5 พฤศจิกายน 2561
Institutional Review Board Number; IRB00007346
Federal Wide Assurance; FWA00002250

สำนักงานจริยธรรมการวิจัย สถาบันสุขภาพเด็กแห่งชาติมหาราชินี
อาคารสถาบันสุขภาพเด็กแห่งชาติมหาราชินี ชั้น 12
420/8 ถนนราชวิถี แขวงทุ่งพญาไท เขตราชเทวี กรุงเทพฯ 10400
โทร. 1415 ต่อ 5210, 5211

Appendix E: Worksheet using for simulations.

SCr level (mg/dL)	N	Time (h)	Dose (mg of CBA/kg)	CR_{av} (mg/dL)	CR_{sd}	$CR_{variance}$	MD (mg of CBA/kg)	InfTime (h)	ADDL (doses)	II (h)
0.10-0.20	27	0	5	0.17	0.03	0.0009	2.5	0.5	4	12
		0	5	0.17	0.03	0.0009	3.75	0.5	4	12
		0	5	0.17	0.03	0.0009	5	0.5	4	12
		0	6.25	0.17	0.03	0.0009	6.25	0.5	4	12
0.21-0.30	32	0	5	0.26	0.03	0.0009	2.5	0.5	4	12
		0	5	0.26	0.03	0.0009	3.75	0.5	4	12
		0	5	0.26	0.03	0.0009	5	0.5	4	12
		0	6.25	0.26	0.03	0.0009	6.25	0.5	4	12
0.31-0.40	9	0	5	0.35	0.03	0.0009	2.5	0.5	4	12
		0	5	0.35	0.03	0.0009	3.75	0.5	4	12
		0	5	0.35	0.03	0.0009	5	0.5	4	12
		0	6.25	0.35	0.03	0.0009	6.25	0.5	4	12
0.41-0.50	5	0	5	0.45	0.02	0.0004	2.5	0.5	4	12
		0	5	0.45	0.02	0.0004	3.75	0.5	4	12
		0	5	0.45	0.02	0.0004	5	0.5	4	12
		0	6.25	0.45	0.02	0.0004	6.25	0.5	4	12
0.51-0.75	6	0	5	0.66	0.09	0.0081	2.5	0.5	4	12
		0	5	0.66	0.09	0.0081	3.75	0.5	4	12
		0	5	0.66	0.09	0.0081	5	0.5	4	12
		0	6.25	0.66	0.09	0.0081	6.25	0.5	4	12

ADDL, number of additional doses; av, average; CR, serum creatinine; II, dosing interval; InfTime, infusion time; MD, maintenance dose; sd, standard deviation.

Appendix F: Codes for model simulations.

```
1  test(){
2      deriv(A1 = -Cl * A1)
3      dosepoint(A1)
4      C = A1 / V
5      error(CEps = 0.306)
6      observe(CObs = C * (1 + CEps))
7      stparm(V = tvV * exp(nV))
8      stparm(Cl = tvCl * CREATININE^dCldCREATININE * exp(nCl))
9      //fcovariate(SEX())
10     //fcovariate(AGE)
11     //fcovariate(WT)
12     //fcovariate(HT)
13
14     //fcovariate(CLCR)
15     //fcovariate(ALBUMIN)
16     //fcovariate(HCT)
17     fixef(tvV = c(, 0.658, ))
18     fixef(tvCl = c(, 0.069, ))
19     //fixef(dVdAGE(enable=c(0)) = c(, 0, ))
20     //fixef(dCldAGE(enable=c(1)) = c(, 0, ))
21     //fixef(dVdCREATININE(enable=c(2)) = c(, 0, ))
22     fixef(dCldCREATININE(enable=c(3)) = c(, -0.53, ))
23     //fixef(dVdCLCR(enable=c(4)) = c(, 0, ))
24     //fixef(dCldCLCR(enable=c(5)) = c(, 0, ))
25     //fixef(dVdWT(enable=c(6)) = c(, 0, ))
26     //fixef(dCldWT(enable=c(7)) = c(, 0, ))
27     ranef(block(nV, nCl) = c(0.300, 0, 0.337))
28     covariate(CRav,CRsd)
29
30     stparm(CREATININE  = CRav + CRsd * nCR)
31     ranef(diag(nCR)(freeze)  = c(0.0009))
32
33
34 }
35
```

Note: Value of ηCR in line 31 was changed in accordance with the different serum creatinine levels.

Appendix G: Published manuscript entitled " No Increased Acute Kidney Injury Rate Through Giving an Intravenous Colistin Loading Dose in Pediatric Patients"

International Journal of Infectious Diseases 106 (2021) 91–97

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

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

No increased acute kidney injury rate through giving an intravenous colistin loading dose in pediatric patients

Noppadol Wacharachaisurapol[a], Surinda Kawichai[b], Ankanee Chanakul[c], Thanyawee Puthanakit[b,d,*]

[a] Clinical Pharmacokinetics and Pharmacogenomics Research Unit, Department of Pharmacology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
[b] Center of Excellence for Pediatric Infectious Diseases and Vaccines, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
[c] Division of Pediatric Nephrology, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
[d] Division of Infectious Diseases, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

ARTICLE INFO

Article history:
Received 1 February 2021
Received in revised form 16 March 2021
Accepted 18 March 2021

Keywords:
Colistin
Loading dose
Nephrotoxicity
Acute kidney injury
Pediatric

ABSTRACT

Objectives: A colistin loading dose is required to achieve adequate drug exposure for the treatment of multidrug-resistant Gram-negative bacteria. However, data on acute kidney injury (AKI) rates associated with this approach in children have been unavailable. The aim of this study was to examine AKI rates in children who were prescribed a colistin loading dose.

Methods: A retrospective study was conducted in patients aged 1 month to 18 years who had received intravenous colistin for ≥48 h. Loading dose (LD) was defined as colistin methanesulfonate at 4–5 mg of colistin base activity/kg/dose. AKI was defined according to KDIGO serum creatinine (SCr) criteria — SCr ≥ 1.5 times the baseline, measured 3–7 days after colistin initiation. Augmented renal clearance (ARC) was defined as an estimated glomerular filtration rate (eGFR) >150 mL/min/1.73 m^2. The rates of AKI were compared between children receiving or not receiving an LD, and between different eGFR groups.

Results: In total, 181 children were enrolled. The mean age was 4.3 years (95% confidence interval [CI], 3.6–4.9 years). Ninety-five of the subjects (52.5%) were male. There were 157 children with a baseline eGFR of ≥ 80 mL/min/1.73 m^2. The overall AKI rate within the first week in this group was 20.4% (95% CI, 14.4–27.6%): LD, 16.1% vs no LD, 23.2% ($p = 0.29$). Subgroup analysis, excluding patients with ARC, showed a lower AKI rate of 12.8% (95% CI, 6.8–21.3%): LD, 9.7% vs no LD, 14.3% ($p = 0.53$).

Conclusions: AKI rate was not different among children who received an intravenous colistin loading dose. This approach should be implemented to ensure the necessary drug exposure required for good treatment outcomes.

Introduction

Multidrug-resistant Gram-negative bacteria (MDR-GNB) are the major cause of hospital-associated infections. The appearance of carbapenem-resistant strains of MDR-GNB, including *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and Enterobacteriaceae, is increasing globally. In Thailand, *A. baumannii*, *P. aeruginosa*, and *Klebsiella pneumoniae* are resistant to carbapenems in up to 81%, 25%, and 17% of cases, respectively (National Antimicrobial Resistance Surveillance Center Thailand, 2019). King Chulalongkorn Memorial Hospital, a leading teaching university hospital in Bangkok, has reported twice the rate of carbapenem-resistant *P. aeruginosa* (49%) and *K. pneumoniae* (36%) compared with the national data. The current treatment of carbapenem-resistant organisms requires a combination of antibiotics. Colistin (polymyxin E) is one of the last resorts for use in combinations. The available parenteral formulation of colistin is colistimethate sodium, also known as colistin methanesulfonate (CMS) (Falagas and Kasiakou, 2006). This is hydrolyzed by blood esterases to the active forms (colistin A, B) (Nakwan et al., 2016). Administering a colistin loading dose is essential to achieve a pharmacokinetic/pharmacodynamic target within 24 h (Nation et al., 2017; Wacharachaisurapol et al., 2020). Nephrotoxicity is a common adverse effect of colistin. In adults, the acute kidney injury (AKI)

* Corresponding author at: Division of Infectious Diseases, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, 1873 Rama IV Road, Pathumwan, Bangkok 10330, Thailand.
E-mail address: Thanyawee.P@chula.ac.th (T. Puthanakit).

https://doi.org/10.1016/j.ijid.2021.03.059
1201-9712/

rate was reported as 51% in patients using colistin, while in the matched controls the AKI rate was 22% (Miano et al., 2018). In children, the nephrotoxicity rate has been reported over a range from 0 to 22.8%, based on various nephrotoxicity definitions (Falagas et al., 2009a; İşgüder et al., 2016; Kapoor et al., 2013; Karbuz et al., 2014; Karli et al., 2013; Paksu et al., 2012; Sahbudak Bal et al., 2018; Tamma et al., 2013). The nephrotoxicity usually occurred when colistin was given concomitantly with other, more nephrotoxic drugs, such as vancomycin or aminoglycosides (Rattanaumpawan et al., 2011). However, there is no study on AKI rate resulting from a loading dose of CMS in pediatric patients. The primary objective of this study was to describe the AKI rates among pediatric patients who were prescribed an intravenous colistin loading dose in comparision with the standard initial dose. The secondary objective was to identify other associated factors affecting these AKI rates.

Materials and methods

Study design

This retrospective study was conducted at King Chulalongkorn Memorial Hospital, Bangkok, Thailand. Pediatric patients who had been prescribed intravenous colistin were identified by searching the pharmacy unit database. Generic names of colistin (colistin, colistimethate sodium, colistin methanesulfonate, CMS) were used for searching the data on patients aged ≤18 years between January 2014 and December 2019. Eligibility criteria included: (i) aged 1 month to 18 years; (ii) received intravenous colistin for ≥48 h; and (iii) available results for baseline serum creatinine (SCr) and levels at follow-up measured 3–7 days after colistin initiation. Premature infants <37 weeks and those receiving renal replacement therapy (RRT) or extracorporeal membrane oxygenation (ECMO) prior to colistin initiation were excluded. This study was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University (IRB no. 177/63).

Definitions

Colistin loading dose was defined as an intravenous CMS injection of at least 4–5 mg of colistin base activity (CBA)/kg/dose. Baseline SCr was defined as SCr level measured less than 48 h before colistin initiation. Follow-up SCr was defined as a SCr at days 3–7 after colistin initiation, and weekly SCr for 3 further consecutive weeks (if available). If there was more than one SCr value in the period, the highest SCr value was chosen. All SCr levels were measured using an enzymatic method in the Clinical Pathology Laboratory, King Chulalongkorn Memorial Hospital. The eGFR was calculated using the modified Schwartz equation: eGFR = $k \times$ Ht/SCr, k = 0.413 (Schwartz et al., 2009) for all patients. In patients with eGFR ≥80 mL/min/1.73 m^2, AKI was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) SCr criteria (Khwaja, 2012): Stage 1 AKI was defined as an increase in follow-up SCr equivalent to >1.5–1.9 times baseline. Stage 2 AKI was defined as follow-up SCr of >2.0–2.9 times baseline. Stage 3 AKI was defined as follow-up SCr of >3 times baseline or a requirement for RRT.

Urine output criteria were not applied in this study because the retrospective documentation was less reliable in this regard, and drug-induced AKI is unlikely to cause oliguria (Miano et al., 2018). In infants and young children aged 1 month to 2 years who are at risk for AKI, pRIFLE criteria are more sensitive (Sutherland et al., 2015); these were also used for AKI diagnosis and compared with the KDIGO SCr criteria. In patients with eGFR <80 mL/min/1.73 m^2, who were considered as having impaired kidney function before colistin initiation, were considered to have deteriorated kidney function when the follow-up SCr increased to >1.5 times baseline. Augmented renal clearance (ARC) was defined as a baseline eGFR > 150 mL/min/1.73 m^2 (Van Der Heggen et al., 2019). In patients who developed AKI, recovery from AKI was defined as a follow-up SCr of <1.5 times baseline.

Antibiotic resistance patterns were reported in terms of: multidrug resistance (MDR), defined as resistance to ≥3 classes of antibiotic; extensive drug resistance (XDR), defined as resistance to all but one or two classes of antibiotic; pandrug resistance (PDR), defined as resistance to all antibiotics tested; carbapenem resistance (CR), defined as resistance to at least one carbapenem and reported separately from MDR, XDR, and PDR patterns. Colistin MIC was performed by Etest (BioMérieux, Marcy l'Étoile, France) in the microbiology unit, King Chulalongkorn Memorial Hospital.

Empirical treatment was defined as a colistin-prescribing indication according to the clinical syndromes and before knowing microbiological data. Targeted treatment was defined as a colistin-prescribing indication according to the known microbiological result of MDR-GNB. Thirty-day mortality was defined as death from any cause occurring within 30 days after colistin initiation. Patients who were discharged before 30 days were considered as surviving.

Data collection and management

A case record form was created for study purposes. All medical records of the identified cases were reviewed by the investigators. Patient data, including demographics, colistin indication, colistin dosing, serial SCr (baseline and follow-up), microbiological data, and treatment outcomes (renal replacement therapy and 30-day mortality), were extracted manually from electronic medical records to the case record forms.

Data analysis

Categorical variables were analyzed with Pearson's chi-square test or Fisher's exact test, as appropriate, and presented as counts and percentages. Continuous variables were analyzed with t-tests and presented as mean with 95% confidence interval (CI) and/or median with interquartile range (IQR). Factors associated with AKI were assessed using univariable and multivariable logistic regression, and presented using odds ratios and 95% CI, with Z-test p-values. Factors with an association of $p < 0.1$ in univariable analysis were selected for further multivariable analysis. The different initial doses of colistin treatment of interest were included in the multivariable model for adjusting the association with AKI. Stata/SE version 13.0 was used for all data analyses.

Results

Patient demographics

Of the 216 children aged 1 month to 18 years, who received colistin between January 2014 and December 2019, 35 were excluded: eight were premature neonates; 21 had received RRT, and six had received ECMO prior to colistin initiation. In total, 181 children were eligible for this study. Of these patients, 95 (52.5%) were male, and the mean age was 4.3 years (95% CI, 3.6–4.9 years); 164 (90.6%) had at least one comorbidity and 155 (85.6%) were admitted to intensive care units (ICU). The most common comorbidity was malignancy (24.9%). For the first dose of colistin, 70 patients (38.7%) received a loading dose and 111 (61.3%) received a standard initial dose (no loading dose). The proportion of patients receiving a colistin loading dose increased from 10.5% during 2014–2017 to 86.6% during 2018–2019, in accordance with the institutional guidelines for colistin dosing for pediatric patients launched in the third quarter of 2017. Patient demographics

according to the first dose of intravenous colistin are shown in Table 1.

Microbiological data

Of the 181 included patients, 92 (50.8%) were prescribed colistin as a targeted treatment for a catheter-related bloodstream infection, lower respiratory tract infection, urinary tract infection, surgical site infection, or intra-abdominal infection. Ninety-six specimens obtained from 92 patients grew *A. baumannii* (*n* = 68; MDR = 8, 11.8%; XDR = 20, 29.4%; PDR = 36, 52.9%; CR = 61, 89.7%), *P. aeruginosa* (*n* = 13; MDR = 4, 30.8%; XDR = 3, 23.1%; PDR = 3, 23.1%; CR = 9, 69.2%), and Enterobacteriaceae (*E. coli and K. pneumoniae*) (*n* = 15; MDR = 2, 13.3%; XDR = 9, 60.0%; PDR = 3, 20.0%; CR = 9, 60.0%). Twenty-four isolates underwent colistin MIC assays using Etest (BioMérieux, Marcy l'Étoile, France). The MIC distribution was 0.75 mg/L (20.8%), 1 mg/L (8.3%), 1.5 mg/L (33.3%), and 2 mg/L (37.5%).

Colistin dose and duration

The mean colistin loading dose was CMS 4.3 mg of CBA/kg/dose (95% CI, 4.1–4.5 mg of CBA/kg/dose). The mean colistin maintenance dose was CMS 5.1 mg of CBA/kg/day (95% CI, 5.0–5.2 mg of CBA/kg/day). The mean duration of colistin therapy among patients receiving colistin as targeted treatment (*n* = 92) was longer than for those receiving colistin as empirical treatment (*n* = 89) (12.6 days; 95% CI, 11.4–13.8 days vs 5.8 days; 95% CI, 5.0–6.6 days; $p < 0.0001$). The mean duration of colistin therapy was similar between patients receiving a loading dose (*n* = 70) or a standard initial dose (*n* = 111) (8.9 days; 95% CI, 7.4–10.4 days vs 9.4 days; 95% CI, 8.3–10.5 days, $p = 0.58$).

Concomitant antibiotics

Concomitant antibiotics were prescribed as one (63.0%), two (30.4%), or three (6.6%) drugs. The concomitant antibiotics included meropenem in 127 patients (70.2%), sulbactam-containing antibiotics (ampicillin/sulbactam, cefoperazone/sulbactam, or sulbactam) in 80 (44.2%), aminoglycosides (amikacin or gentamicin) in 23 (12.7%), fluoroquinolones (ciprofloxacin or levofloxacin) in 15 (8.3%), and other antibiotics in 15 (8.3%).

Acute kidney injury rates and recovery

Data on SCr were available for all patients (*n* = 181) at the 1st week after colistin initiation, and for 170 (93.9%), 87 (48.1%), and

Table 1
Patient demographics and medical characteristics classified according to first dose of intravenous colistin.

	Total*N* = 181	Receiving a loading dose*N* = 70	Receiving a standard initial dose*N* = 111	*p*-Value[a]
Age (year)	4.3 (3.6–4.9)	5.1 (3.8–6.4)	3.7 (2.9–4.5)	0.049
1 month–2 years	97 (53.6)	35 (50.0)	62 (55.9)	0.44
>2–18 years	84 (46.4)	35 (50.0)	49 (44.1)	0.44
Male sex	95 (52.5)	30 (42.9)	65 (58.6)	0.04
Weight (kg)	16.0 (13.8–18.1)	18.4 (14.6–22.2)	14.4 (12.0–16.9)	0.07
Baseline eGFR (mL/min/1.73 m^2)	133.3 (124.6–142.0)	144.4 (130.2–158.7)	126.3 (115.4–137.2)	0.045
<80	24 (13.3)	8 (11.4)	16 (14.4)	0.56
80–150	94 (51.9)	31 (44.3)	63 (56.8)	0.10
>150	63 (34.8)	31 (44.3)	32 (28.8)	0.03
Comorbidity[b]	164 (90.6)	62 (88.6)	102 (91.9)	0.46
Malignancy	45 (24.9)	17 (24.3)	28 (25.2)	0.89
Chronic cardiac disease	39 (21.6)	12 (17.1)	27 (24.3)	0.25
Neurological disease	31 (17.1)	13 (18.6)	18 (16.2)	0.68
Chronic pulmonary disease	25 (13.8)	12 (17.1)	13 (11.7)	0.30
Receiving immunosuppressive agent	22 (12.2)	11 (15.7)	11 (9.9)	0.24
Chronic liver diseases	17 (9.4)	7 (10.0)	10 (9.0)	0.82
Others	17 (9.4)	4 (5.7)	13 (11.7)	0.18
Intensive care unit admission	155 (85.6)	59 (84.3)	96 (86.5)	0.68
Colistin indication				
Sepsis/CRBSI/CLABSI	95 (52.5)	40 (57.1)	55 (49.6)	0.33
VAP	66 (36.5)	24 (34.3)	42 (37.8)	0.63
Others[c]	20 (11.0)	6 (8.6)	14 (12.6)	0.40
Overall colistin duration (day)	9.2 (8.4–10.1)	8.9 (7.4–10.5)	9.4 (8.4–10.1)	0.61
Receiving concomitant nephrotoxic drugs within 3 days after colistin initiation	161 (89.0)	61 (87.1)	100 (90.1)	0.54
IV furosemide	110 (60.8)	37 (52.9)	73 (65.8)	0.08
IV vancomycin	89 (49.2)	42 (60.0)	47 (42.3)	0.02
IV aminoglycosides	31 (17.1)	13 (18.6)	18 (16.2)	0.68
IV amphotericin B	18 (9.9)	2 (2.9)	16 (14.4)	0.01
IV acyclovir or IV ganciclovir	17 (9.4)	8 (11.4)	9 (8.1)	0.45
Cyclosporin or tacrolimus	15 (8.3)	7 (10.0)	8 (7.2)	0.51
NSAIDs	1 (0.6)	0	1 (0.9)	1.00
No. of concomitant nephrotoxic drugs being prescribed within 3 days of colistin initiation				
None	20 (11.0)	9 (12.9)	11 (9.9)	0.53
1–2	133 (73.5)	50 (71.4)	83 (74.8)	0.62
≥3	28 (15.5)	11 (15.7)	17 (15.3)	0.94

CLABSI, central line-associated bloodstream infection; CRBSI, catheter-related bloodstream infection; eGFR, estimated glomerular filtration rate; HAP, hospital-associated pneumonia; IV, intravenous; LD, loading dose; NSAIDs, nonsteroidal anti-inflammatory drugs; VAP, ventilator-associated pneumonia.
Data are shown as mean (95% confidence intervals) or *n* (%).
[a] *p*-Value of *t*-test for mean; Pearson's chi-square test or Fisher's exact test for proportions.
[b] Comorbidity summation exceeds 100% owing to some patients having more than one comorbidity.
[c] Others included urinary tract infection, surgical site infection, and intra-abdominal infection.

39 (21.5%) at the 2nd, 3rd, and 4th weeks, respectively. Overall AKI rates at the 1st week and the 4th week after colistin initiation among patients with eGFR ≥80 mL/min/1.73 m^2 (n = 157) were 20.4% (32/157) and 29.3% (46/157), respectively. Comparisons of AKI rates between patients receiving or not receiving a colistin loading dose are shown in Figure 1A and B.

Among 46 patients who developed AKI, stage 1 AKI was the most common (n = 31, 67.4%). AKI mostly developed within the first week (n = 32, 69.6%). Seven children died with associated multiorgan failure, while 39 children recovered from AKI with a mean time to recovery of 8.7 days (95% CI, 6.6–10.8 days). No patient underwent renal replacement therapy.

Among 24 patients with impaired kidney function at baseline, two (8.3%) developed deteriorated kidney function within the 1st week after colistin initiation. One of these received peritoneal dialysis. However, both of them died due to underlying disease involving complex congenital heart anomalies.

Augmented renal clearance may cause falsely low SCr readings at baseline, meaning that our definition of 1.5 times SCr may cause bias towards a high rate of AKI. Therefore, we analyzed a subset of data that included only patients with a baseline eGFR of 80–150 mL/min/1.73 m^2 (n = 94). Overall AKI rates at the 1st week and 4th week after colistin initiation were 12.8% (12/94) and 21.3% (20/94), respectively. Stage 1 AKI remained the most common (n = 13, 65.0%). Comparisons of AKI rates between patients receiving or not receiving a colistin loading dose are shown in Figure 1C and D.

In infants and young children aged 1 month to 2 years, which formed the majority in this study and seem to be a risk group for AKI (Table 2), we analyzed the AKI rate using more sensitive criteria (pRIFLE) and found no significant difference between KDIGO and pRIFLE in AKI rate (36% vs 40%).

Associated factors of AKI

Comparative analyses between patients with or without AKI are shown in Table 2. Receiving a colistin loading dose was not associated with an increase in AKI rate. However, receiving ≥3 concomitant nephrotoxic drugs was associated with an increase in AKI rate.

Treatment outcomes

Of 181 patients, one (0.6%) with impaired kidney function before colistin initiation received renal replacement therapy. Twenty patients died within 30 days after colistin initiation, resulting in a 30-day mortality rate of 11.0%. Ten fatality cases (50.0%) were associated with MDR–GNB infections (ventilator-associated pneumonia, n = 7; bloodstream infection, n = 1; intra-abdominal infection, n = 1; surgical site infection with meningitis, n = 1), while ten (50.0%) were associated with the underlying diseases or other infections (congenital heart disease, n = 4; malignancy, n = 2; cirrhosis with liver failure, n = 1; *Pneumocystis jirovecii* pneumonia with respiratory failure, n = 2; invasive pulmonary aspergillosis with pulmonary hemorrhage, n = 1).

Discussion

Our study explored the association between administration of an intravenous colistin loading dose and AKI rate in pediatric patients. The rates of AKI within the 1st week were 16.1% and 23.2% for those who received a loading dose and a standard initial dose, respectively. Among patients with AKI, two-thirds of cases occurred within the 1st week, and two-thirds of these were stage 1 AKI, with a reversible condition. The significantly associated factor for AKI in the pediatric population was concomitant nephrotoxic drugs.

Nephrotoxicity is known to be a common adverse drug reaction caused by colistin, with a variety of associated conditions, such as cylindruria, hematuria, proteinuria, and elevated blood urea nitrogen or serum creatinine (Falagas et al., 2009b). However, nephrotoxicity reported in the literature is mostly based on SCr-associated criteria, including elevation of SCr and a decline in creatinine clearance or eGFR (Falagas et al., 2009a; Kapoor et al., 2013; Karbuz et al., 2014; Karli et al., 2013; Paksu et al., 2012;

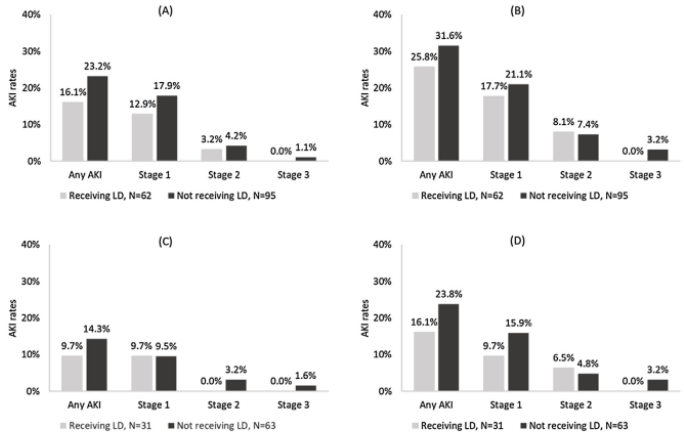


Figure 1. Comparisons of acute kidney injury (AKI) rates between patients receiving or not receiving a colistin loading dose (LD): (A) within the first week after colistin initiation; (B) within 4 weeks after colistin initiation; (C) within the first week after colistin initiation, excluding patients with augmented renal clearance; (D) within 4 weeks after colistin initiation, excluding patients with augmented renal clearance. There were no significant differences among patients receiving or not receiving LD; all p-values > 0.05. AKI was staged according to the Kidney Disease: Improving Global Outcomes (KDIGO) serum creatinine criteria.

Table 2
Association of characteristics at baseline and during intravenous colistin treatment with acute kidney injury in pediatric patients without impaired kidney function at baseline.

	Total	With AKI *n* (%)	Crude OR (95% CI)	*p*-Value	Adjusted OR (95% CI)	*p*-Value
Total	157	46 (29.3)				
First dose of colistin treatment						
Loading dose	62	16 (25.8)	1		1	
Standard dose	95	30 (31.6)	1.33 (0.65–2.71)	0.44	1.30 (0.61–2.77)	0.49
Colistin treatment duration in days						
1–7	79	23 (29.1)	1			
8–14	50	13 (26.0)	0.84 (0.38–1.86)	0.67		
15–30	28	10 (35.7)	1.33 (0.53–3.31)	0.54		
Age						
>2–18 years	82	19 (23.2)	1		1	
1 month–2 years	75	27 (36.0)	1.86 (0.93– 3.74)	0.08	1.83 (0.88–3.81)	0.10
Gender						
Female	77	21 (27.3)	1			
Male	80	25 (31.2)	1.21 (0.61–2.41)	0.58		
Comorbidity						
No	16	3 (18.7)	1			
Yes	141	43 (30.5)	1.90 (0.52–7.02)	0.34		
Colistin indication						
Others[a]	19	3 (15.8)	1		1	
Sepsis/CRBSI/CLABSI	82	22 (26.8)	1.96 (0.52, 7.37)	0.32	1.87 (0.45–7.73)	0.39
VAP	56	21 (37.5)	3.2 (0.83, 12.30)	0.09	3.62 (0.85–15.41)	0.08
No. of concomitant nephrotoxic drugs being prescribed within 3 days of colistin initiation						
0	15	1 (6.7)	1		1	
1–2	116	33 (28.4)	5.57 (0.70–44.04)	0.10	5.25 (0.63–43.88)	0.13
≥3	26	12 (46.2)	12.00 (1.37–105.13)	0.02	13.99 (1.49–131.63)	0.02

AKI, acute kidney injury; CI, confidence interval; CLABSI, central line-associated bloodstream infection; CRBSI, catheter-related bloodstream infection; OR, odds ratio; VAP, ventilator-associated pneumonia.
[a] Others included urinary tract infection, surgical site infection, and intra-abdominal infection.

Sahbudak Bal et al., 2018; Tamma et al., 2013; Wacharachaisurapol et al., 2020). In this study, we reported nephrotoxicity as AKI defined according to the KDIGO SCr criteria. The overall AKI rate that occurred within the 1st week after colistin initiation was 20.4%. Recently, Kaddourah et al. (2017) conducted a large (n = 4683) prospective, multinational study of the epidemiology of AKI in pediatric and young adult ICU patients with a median age of 66.0 months (IQR, 18.8–151.1 months). The AKI definitions of KDIGO were used. The AKI rate within the 1st week after ICU admission was as high as 26.9%. Among those with AKI, more than half (56.9%) were stage 1. In our study, almost all of the patients (85.6%) were admitted to ICU. Thus, our patients' status was similar to that of the patients in the Kaddourah et al. study. The AKI rates and stage 1 AKI were comparable (20.4% vs 26.9%, p = 0.07 and 15.9% vs 15.3%, p = 0.84). However, severe (stage 2 and stage 3) AKI was less common in our study (4.5% vs 11.6%, p = 0.005).

Table 3
Comparison of characteristics and reported nephrotoxicity rates among studies of critically ill pediatric patients receiving intravenous colistin.

Study	No. of patients	Age[a] (years)	Colistin dose[a] (mg of CBA/kg/day)	Duration of colistin[a] (days)	Nephrotoxicity % (no. of cases)	Nephrotoxicity definition
Nephrotoxicity defined as an increase of SCr to >1.5–2 times baseline						
Falagas et al. (2009a)	7	11 (1.2–13)	Fixed dose, 2.1	10 (min–max, 2–23)	0	SCr > 1.5 times or > 1.3 mg/dL
Karbuz et al. (2014)	29 (38 courses)	1.4 (0.3–18)	2.5 (1.7–2.7) or 5.0 (2.3–5.6)	12 (2–37)	2.6 (1/38)	SCr > 2 times or SCr > normal value
Ozsurekci et al. (2016)	64 (73 courses)	2.5 (0.7–10.5)	N/A	17.0 (12.0–30.0)	4.1 (3/73)	SCr > 2 times
Sahbudak Bal et al. (2018)	94 (104 courses)	Median, 4.7	5.0[b]	12.5 ± 6.4	10.5 (11/104)	SCr > 1.5 times
Present study, 2021						
Patients with baseline eGFR ≥ 80 mL/min/1.73 m^2	157	2.2 (0.8–8.0)	5.2 ± 0.7	9.1 ± 5.9	20.4[c] (32/157)	SCr > 1.5 times
Excluded patients with ARC	94	1.6 (0.7–6.8)	5.2 ± 0.9	8.9 ± 5.3	12.8[c] (12/94)	SCr > 1.5 times
Nephrotoxicity defined as a decrease in Cl_{Cr} or an increase in SCr						
Karli et al. (2013)	31 (41 courses)	3 (min–max, 0.3–17.0)	4.9 ± 0.5[b]	19.8 ± 10.3	7.3 (3/41)	Decreased Cl_{Cr} > 50% or SCr > 1.1 mg/dL
Kapoor et al. (2013)	50	3.0 (0.1–12)	1.7–2.5	Mean, 14.3 (range, 7–21)	10.0 (5/50)	Decreased Cl_{Cr} > 30% or SCr > 2 times
Paksu et al. (2012)	79 (87 courses)	2.5 (0.3–18.0)	2.25 ± 0.25	17.2 ± 8.4	2.3 (2/87)	Decreased Cl_{Cr} > 50% or SCr > 1.1 mg/dL
Tamma et al. (2013)	92	16 (11–17.5)	5[b] (non-cystic fibrosis) or 7.5 (cystic fibrosis)	N/A	22.8 (21/92)	Cl_{Cr} ≤ 60 mL/min or decrease in category of clearance

ARC, augmented renal clearance (eGFR > 150 mL/min/1.73 m^2); CBA, colistin base activity; Cl_{Cr}, creatinine clearance; N/A, not available; SCr, serum creatinine.
[a] Data are shown as mean ± standard deviation or median (range), or described otherwise.
[b] No available data on whether it was mg of CBA or colistin methanesulfonate.
[c] Nephrotoxicity rate within the first week after intravenous colistin initiation.

The AKI rates reported among pediatric studies evaluating colistin efficacy and safety ranged from 0 to 22.8% (Falagas et al., 2009a; İşgüder et al., 2016; Kapoor et al., 2013; Karbuz et al., 2014; Karli et al., 2013; Paksu et al., 2012; Sahbudak Bal et al., 2018; Tamma et al., 2013), while the rate was found to be as high as 51% in an adult study (Miano et al., 2018). Among pediatric studies, the differing AKI rates were probably caused by many factors, such as patient characteristics, number of patients studied, AKI definition, and colistin dosing. Comparisons of characteristics and reported nephrotoxicity among studies of pediatric patients receiving intravenous colistin are shown in Table 3. The overall AKI rates found in our study appear to be higher than those in previous studies owing to the stricter AKI definition and the longer AKI follow-up of up to 4 weeks, during which other causes of AKI could be significant confounders. None of the previous pediatric studies reported the association between giving an intravenous colistin loading dose and AKI rate. However, a review from Vardakas et al. (2016) reported a range of AKI rates of 15.6–53% among adult patients receiving a colistin loading dose. In our study, it was found that giving a colistin loading dose did not increase AKI risk. This is consistent with some adult studies showing similar findings (Hassan et al., 2018; Omrani et al., 2015).

For our study, a control group (non-colistin antibiotics) was not available. However, Ozsurekci et al. (2016) reported the nephrotoxicity rates among pediatric patients with MDR or XDR Gram-negative infection who were treated with colistin and non-colistin antibiotics. It was found that there was no significant difference between the two groups. This implied that using colistin did not increase the AKI risk, which was different from an adult study showing an AKI rate of 51% in the colistin group versus 22% in the control group (Miano et al., 2018). The risk factors for nephrotoxicity in patients receiving colistin include concomitant nephrotoxic drugs (e.g., vancomycin, aminoglycosides), liver disease, and low hemoglobin level (Miano et al., 2018; Rattanaumpawan et al., 2011). In our study, a number of concomitant nephrotoxic drugs ≥3 was found to be the significantly associated factor for AKI. AKI developed mostly within the 1st week after colistin initiation (69.6% in our study), which was also the case in previous pediatric studies (90.9–100%) (Sahbudak Bal et al., 2018; Tamma et al., 2013). The majority of cases were stage 1 AKI, which recovered with supportive treatment. Tamma et al. reported only 4.8% of AKI patients needed dialysis (Tamma et al., 2013). No AKI patient in our study required renal replacement therapy. However, one patient with impaired kidney function at baseline required peritoneal dialysis after colistin initiation.

In critically ill patients (e.g., patients with sepsis or burn injuries), ARC commonly occurs, especially in the first few days of illness (Blot et al., 2014). ARC can be as high as 10–67% in critically ill pediatric patients (Huttner et al., 2015; van den Anker et al., 2017; Van Der Heggen et al., 2019). The effects of ARC could be a cause of falsely high AKI rates and low plasma antibiotic concentrations (Huttner et al., 2015; van den Anker et al., 2017; Van Der Heggen et al., 2019; Wacharachaisurapol et al., 2020), as well as ARC-enhanced excretion of serum creatinine and drugs as compared with the baseline owing to glomerular hyperfiltration. The definition of AKI according to the KDIGO SCr criteria is based on a comparison of follow-up vs baseline SCr. The baseline SCr is probably falsely low owing to ARC. This could lead to a falsely high AKI rate. In our study, the baseline SCr used might not have been the true baseline for the patients because it was measured at the start of the illness. In consideration of this issue, a subgroup analysis was performed by excluding patients with probable ARC (eGFR > 150 mL/min/m^2). The overall AKI rate within the 1st week after colistin initiation fell from 20.4% to 12.8%. Concerning the ARC effect on antibiotic levels, the colistin dose recommended by the manufacturer (no loading dose recommended) (US FDA, 2017) for pediatric patients may not be adequate, especially in a setting with a high prevalence of MDR-GNB with increased colistin MIC (Ooi et al., 2019; Wacharachaisurapol et al., 2020), as in our setting. Even though the MIC distribution in our study showed that all 24 isolates with colistin MIC results were colistin-susceptible, based on a susceptibility breakpoint of ≤2 mg/L, as recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (Tsuji et al., 2019), 37.5% were on the cut-off. Moreover, the colistin Etest can produce very major errors (false susceptibility results) of up to 12% for Enterobacteriaceae and 33% for *P. aeruginosa* and *A. baumannii*. Broth microdilution, which is the reference method, should be used for evaluating colistin MIC (Chew et al., 2017; Matuschek et al., 2018).

The current treatment guidelines on using polymixins endorsed by the American College of Clinical Pharmacy (ACCP), Infectious Diseases Society of America (IDSA), International Society of Anti-Infective Pharmacology (ISAP), Society for Critical Care Medicine (SCCM), and Society of Infectious Diseases Pharmacists (SIDP) recommends administering an intravenous colistin loading dose in adult patients to improve drug exposure (Tsuji et al., 2019). Without a loading dose, colistin may take many hours or even days to achieve a steady-state level, especially in critically ill patients (Plachouras et al., 2009). Karageorgos et al. conducted a systematic review on intravenous colistin use for infections due to MDR-GNB in critically ill pediatric patients, and suggested that the absence of a loading dose may have an association with mortality (Karageorgos et al., 2019). From our previous pharmacokinetic study of intravenous colistin, the median $C_{average}$ after giving a loading dose reached the desired level of ≥2 mg/L, which improved drug exposure (Wacharachaisurapol et al., 2020).

Our study has several strengths. It is the first to describe and comparing AKI rates in pediatric patients who were prescribed or were not prescribed a colistin loading dose. The time for AKI follow-up was up to 4 weeks. The overall AKI rate was similar to the rate reported in a large study conducted in pediatric ICU patients. Giving a colistin loading dose did not increase the AKI risk. The associated factors for AKI were also identified.

This study also has some limitations. First, the findings cannot be generalized to the age groups outside the study population, for example in infants <1 month of age. Second, there was no control group of patients who were not prescribed colistin. Thus, the exact AKI rate caused by colistin could not be identified.

In conclusion, the results of this study showed that giving a colistin loading dose of 4–5 mg of CBA/kg/dose did not increase AKI risk. The significant associated factor for developing AKI was receiving ≥3 concomitant nephrotoxic drugs. AKI monitoring using serum creatinine is suggested especially for the first week after colistin initiation, since most AKI cases developed within this period.

Funding

Noppadol Wacharachaisurapol is supported by a scholarship from the 100th Anniversary Chulalongkorn UniversityFund for Doctoral Scholarship and the 90th Anniversary Chulalongkorn UniversityFund (Ratchadaphiseksomphot Endowment Fund).

Ethical approval

This study was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University (IRB no. 177/63).

Conflicts of interest

All authors declare no conflicts of interest for this manuscript.

Author contributions

Noppadol Wacharachaisurapol: conception and design of the study (lead), acquisition of data (lead), analysis and interpretation of the data (support), drafting the article (lead), revising the article (lead), final approval of the version to be submitted (support).

Surinda Kawichai: analysis and interpretation of the data (lead), drafting the article (support), revising the article (support), final approval of the version to be submitted (support).

Ankanee Chanakul: conception and design of the study (support), analysis and interpretation of the data (support), revising the article (support), final approval of the version to be submitted (support).

Thanyawee Puthanakit: conception and design of the study (lead), analysis and interpretation of the data (support), revising the article (lead), final approval of the version to be submitted (lead).

Acknowledgments

The authors would like to thank Watchara Sakares, PharmD (Pharmacy Department, King Chulalongkorn Memorial Hospital, Thai Red Cross Society) for his effort in identifying the pediatric patients who were prescribed colistin in this study.

References

Blot SI, Pea F, Lipman J. The effect of pathophysiology on pharmacokinetics in the critically ill patient—concepts appraised by the example of antimicrobial agents. Adv Drug Deliv Rev 2014;77:3–11.

Chew KL, La MV, Lin RTP, Teo JWP. Colistin and polymyxin B susceptibility testing for carbapenem-resistant and MCR-positive Enterobacteriaceae: comparison of Sensititre, MicroScan, Vitek 2, and Etest with broth microdilution. J Clin Microbiol 2017;55(9):2609–16.

Falagas ME, Kasiakou SK. Use of international units when dosing colistin will help decrease confusion related to various formulations of the drug around the world. Antimicrob Agents Chemother 2006;50(6):2274–5.

Falagas ME, Sideri G, Vouloumanou EK, Papadatos JH, Kafetzis DA. Intravenous colistimethate (colistin) use in critically ill children without cystic fibrosis. Pediatr Infect Dis J 2009a;28(2):123–7.

Falagas ME, Vouloumanou EK, Rafailidis PI. Systemic colistin use in children without cystic fibrosis: a systematic review of the literature. Int J Antimicrob Agents 2009b;33(6) 503.e1–e13.

Hassan MM, Gaifer Z, Al-Zakwani IS. Incidence and risk factors of nephrotoxicity in patients on colistimethate sodium. Int J Clin Pharm 2018;40(2):444–9.

Huttner A, Von Dach E, Renzoni A, Huttner BD, Affaticati M, Pagani L, et al. Augmented renal clearance, low β-lactam concentrations and clinical outcomes in the critically ill: an observational prospective cohort study. Int J Antimicrob Agents 2015;45(4):385–92.

İşgüder R, Ağın H, Ceylan G, Bayram N, Devrim İ. Safety and efficacy of intravenous colistin use for the treatment of nosocomial multidrug-resistant *Acinetobacter baumannii* infections in a pediatric intensive care unit. Am J Infect Control 2016;44(6):734–5.

Kaddourah A, Basu RK, Bagshaw SM, Goldstein SL. Epidemiology of acute kidney injury in critically ill children and young adults. N Engl J Med 2017;376(1):11–20.

Kapoor K, Jajoo M, Dublish S, Dabas V, Gupta S, Manchanda V. Intravenous colistin for multidrug-resistant Gram-negative infections in critically ill pediatric patients. Pediatr Crit Care Med 2013;14(6):e268–72.

Karageorgos SA, Bassiri H, Siakallis G, Miligkos M, Tsioutis C. Intravenous colistin use for infections due to MDR Gram-negative bacilli in critically ill paediatric patients: a systematic review and meta-analysis. J Antimicrob Chemother 2019;74(9):2497–506.

Karbuz A, Ozdemir H, Yaman A, Kocabas BA, Odek C, Guriz H, et al. The use of colistin in critically ill children in a pediatric intensive care unit. Pediatr Infect Dis J 2014;33(1):e19–24.

Karli A, Paksu MS, Karadag A, Belet N, Paksu S, Guney AK, et al. Colistin use in pediatric intensive care unit for severe nosocomial infections: experience of an university hospital. Ann Clin Microbiol Antimicrob 2013;12:32.

Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract 2012;120(4):c179–84.

Matuschek E, Åhman J, Webster C, Kahlmeter G. Antimicrobial susceptibility testing of colistin — evaluation of seven commercial MIC products against standard broth microdilution for *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter* spp. Clin Microbiol Infect 2018;24(8):865–70.

Miano TA, Lautenbach E, Wilson FP, Guo W, Borovskiy Y, Hennessy S. Attributable risk and time course of colistin-associated acute kidney injury. Clin J Am Soc Nephrol 2018;13(4):542–50.

Nakwan N, Usaha S, Chokephaibulkit K, Villani P, Regazzi M, Imberti R. Pharmacokinetics of colistin following a single dose of intravenous colistimethate sodium in critically ill neonates. Pediatr Infect Dis J 2016;35(11):1211–4.

Nation RL, Garonzik SM, Thamlikitkul V, Giamarellos-Bourboulis EJ, Forrest A, Paterson DL, et al. Dosing guidance for intravenous colistin in critically-ill patients. Clin Infect Dis 2017;64(5):565–71.

National Antimicrobial Resistance Surveillance Center Thailand. Percentage of susceptible organisms isolated from all specimen, 85 hospitals, Jan–Dec 2018. 2019 Available from: http://narst.dmsc.moph.go.th/antibiograms/2018/12/Jan-Dec2018-All.pdf. [Accessed 23 October 2020].

Omrani AS, Alfahad WA, Shoukri MM, Baadani AM, Aldalbahi S, Almitwazi AA, et al. High dose intravenous colistin methanesulfonate therapy is associated with high rates of nephrotoxicity; a prospective cohort study from Saudi Arabia. Ann Clin Microbiol Antimicrob 2015;14:3.

Ooi MH, Ngu SJ, Chor YK, Li J, Landersdorfer CB, Nation RL. Population pharmacokinetics of intravenous colistin in pediatric patients: implications for the selection of dosage regimens. Clin Infect Dis 2019;69(11):1962–8.

Ozsurekci Y, Aykac K, Cengiz AB, Bayhan C, Sancak B, Karadag Oncel E, et al. Is colistin effective in the treatment of infections caused by multidrug-resistant (MDR) or extremely drug-resistant (XDR) gram-negative microorganisms in children?. Diagn Microbiol Infect Dis 2016;85(2):233–8.

Paksu MS, Paksu S, Karadag A, Sensoy G, Asilioglu N, Yildizdas D, et al. Old agent, new experience: colistin use in the paediatric intensive care unit — a multicentre study. Int J Antimicrob Agents 2012;40(2):140–4.

Plachouras D, Karvanen M, Friberg LE, Papadomichelakis E, Antoniadou A, Tsangaris I, et al. Population pharmacokinetic analysis of colistin methanesulfonate and colistin after intravenous administration in critically ill patients with infections caused by Gram-negative bacteria. Antimicrob Agents Chemother 2009;53(8):3430–6.

Rattanaumpawan P, Ungprasert P, Thamlikitkul V. Risk factors for colistin-associated nephrotoxicity. J Infect 2011;62(2):187–90.

Sahbudak Bal Z, Kamit Can F, Yazici P, Berna Anil A, Duyu M, Yilmaz Ciftdogan D, et al. The evaluation of safety and efficacy of colistin use in pediatric intensive care unit: results from two reference hospitals and review of literature. J Infect Chemother 2018;24(5):370–5.

Schwartz GJ, Munoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol 2009;20(3):629–37.

Sutherland SM, Byrnes JJ, Kothari M, Longhurst CA, Dutta S, Garcia P, et al. AKI in hospitalized children: comparing the pRIFLE, AKIN, and KDIGO definitions. Clin J Am Soc Nephrol 2015;10(4):554–61.

Tamma PD, Newland JG, Pannaraj PS, Metjian TA, Banerjee R, Gerber JS, et al. The use of intravenous colistin among children in the United States: results from a multicenter, case series. Pediatr Infect Dis J 2013;32(1):17–22.

Tsuji BT, Pogue JM, Zavascki AP, Paul M, Daikos GL, Forrest A, et al. International Consensus Guidelines for the Optimal Use of the Polymyxins: endorsed by the American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Society of America (IDSA), International Society for Anti-infective Pharmacology (ISAP), Society of Critical Care Medicine (SCCM), and Society of Infectious Diseases Pharmacists (SIDP). Pharmacotherapy 2019;39(1):10–39.

US FDA. Coly-Mycin® M Parenteral (Colistimethate for Injection, USP). 2017 Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/050108s033lbl.pdf. [Accessed 12 November 2020].

van den Anker JN, Knibbe CAJ, Tibboel D. Augmented renal clearance in critically ill pediatric patients: does it impact the outcome of pharmacotherapy?. Pediatr Crit Care Med 2017;18(9):901–2.

Van Der Heggen T, Dhont E, Peperstraete H, Delanghe JR, Vande Walle J, De Paepe P, et al. Augmented renal clearance: a common condition in critically ill children. Pediatr Nephrol 2019;34(6):1099–106.

Vardakas KZ, Rellos K, Triarides NA, Falagas ME. Colistin loading dose: evaluation of the published pharmacokinetic and clinical data. Int J Antimicrob Agents 2016;48(5):475–84.

Wacharachaisurapol N, Phasomsap C, Sukkummee W, Phaisal W, Chanakul A, Wittayalertpanya S, et al. Greater optimisation of pharmacokinetic/pharmacodynamic parameters through a loading dose of intravenous colistin in paediatric patients. Int J Antimicrob Agents 2020;55(6)105940.

Appendix H: Accepted manuscript entitled “Dose recommendations for intravenous colistin in pediatric patients from a prospective, multicenter, population pharmacokinetic study”

From: em.theijid.161c.742cd5.e6230bc3@editorialmanager.com <em.theijid.161c.742cd5.e6230bc3@editorialmanager.com> on behalf of Eskild Petersen <em@editorialmanager.com>
Sent: Thursday, June 24, 2021 2:43 AM
To: Thanyawee Puthanakit
Subject: Manuscript Decision THEIJID-D-21-01642R1

Manuscript Number: THEIJID-D-21-01642R1
Article Title: Dose recommendations for intravenous colistin in pediatric patients from a prospective, multicenter, population pharmacokinetic study.

Corresponding Author: Dr. Thanyawee Puthanakit
International Journal of Infectious Diseases

23 Jun 2021

Dear Dr. Puthanakit,

I am pleased to tell you that your work has now been accepted for publication in the International Journal of Infectious Diseases, and will be forwarded to the Production department for typesetting. Proofs for approval will be sent to the corresponding author within the next 3 weeks.

We appreciate and value your contribution to International Journal of Infectious Diseases. We regularly invite authors of recently published manuscript to participate in the peer review process. If you were not already part of the journal's reviewer pool, you have now been added to it. We look forward to your continued participation in our journal, and we hope you will consider us again for future submissions.

Thank you for submitting your work to the journal.

Kind regards,

Eskild Petersen, MD, DMSc, MBA
Editor-in-Chief
International Journal of Infectious Diseases

Title: Dose recommendations for intravenous colistin in pediatric patients from a prospective, multicenter, population pharmacokinetic study.

Author names

Noppadol Wacharachaisurapol[a], Warumphon Sukkummee[a], Orawan Anunsittichai[b], Panida Srisan[c], Siriporn Sangkhamal[d], Prawat Chantharit[e], Warunee Punpanich Vandepitte[f], Thitima Wattanavijitkul[g], Thanyawee Puthanakit[b, h]

Affiliations

[a] Clinical Pharmacokinetics and Pharmacogenomics Research Unit, Department of Pharmacology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
[b] Centre of Excellence for Pediatric Infectious Diseases and Vaccines, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
[c] Division of Pulmonary and Critical Care, Department of Pediatrics, Queen Sirikit National Institute of Child Health, Bangkok, Thailand.
[d] Pediatric Intensive Care Unit, Queen Sirikit National Institute of Child Health, Bangkok, Thailand.
[e] Division of Infectious Diseases, Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand
[f] Queen Sirikit National Institute of Child Health, Bangkok, Thailand; College of Medicine, Rangsit University, Bangkok, Thailand.
[g] Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok, Thailand.
[h] Division of Infectious Diseases, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

Running title: Colistin Dose Recommendations in Pediatrics

Corresponding Author: Thanyawee Puthanakit, M.D.

Division of Infectious Diseases, Department of Pediatrics,

Faculty of Medicine, Chulalongkorn University

1873 Rama IV Road, Pathumwan, Bangkok, Thailand, 10330

Email: thanyawee.p@chula.ac.th

Telephone: +6622564930

Abstract

Objectives: We aimed to describe population pharmacokinetics of intravenous colistin use in children and propose optimal dosage regimens.

Methods: A prospective, multicenter, population pharmacokinetic (PPK) study was conducted. Phoenix™ 64 version 8.3 was used for PPK analysis. Simulations were performed to estimate the probability of target attainment of patients achieving target plasma colistin average steady-state concentrations ($C_{ss,avg}$).

Results: A total of 334 plasma colistin concentrations were obtained from 79 pediatric patients with a median age (interquartile range) of 2.6 years (0.8–6.8 years); 73 (92.4%) were admitted to intensive care units. Colistin pharmacokinetics were adequately described by a one-compartment model with first-order elimination along with serum creatinine (SCr) as a significant covariate on colistin clearance. The simulation demonstrated that the recommended dose of 5 mg of colistin base activity (CBA)/kg/day resulted in 18.2–63.0% probability to achieve a target $C_{ss,avg}$ of 2 mg/L. With a lower targeted $C_{ss,avg}$ of 1 mg/L, colistin dosing with 7.5 and 5 mg of CBA/kg/day were adequate for children with SCr levels of 0.1–0.3 and >0.3 mg/dL, respectively.

Conclusions: SCr is a significant covariate on colistin clearance in children. Colistin dosing should be selected regarding the patient's SCr level and the desired target $C_{ss,avg}$.

Keywords: Colistin; Pharmacokinetics; Pediatrics; Multidrug-resistant bacteria

Introduction

The global burden of multidrug-resistant Gram-negative bacteria (MDR-GNB) is increasing rapidly (World Health Organization, 2017). In Thailand, the rates of carbapenem-resistant Gram-negative bacteria are as high as 60% of *Acinetobacter baumannii*, 30% of *Pseudomonas aeruginosa*, and 10% of *Klebsiella pneumoniae* (National Antimicrobial Resistance Surveillance Center of Thailand (NARST), 2021). The treatment of carbapenem-resistant Gram-negative bacteria requires use of a combination of antibiotics, including colistin. Currently, colistin is available in a prodrug formulation, colistimethate sodium, also known as colistin methanesulfonate (CMS) (Falagas and Kasiakou, 2006). CMS dosage is currently recommended at 2.5–5 mg of colistin base activity (CBA)/kg/day (European Medicines Agency, 2014, US FDA, 2017) and is weight-based derived from adult studies (Ooi et al., 2019, US FDA, 2017) due to the paucity of pharmacokinetic (PK) data in children at the time. Recently, studies of colistin pharmacokinetics in both neonates (Nakwan et al., 2016), infants and older children (Antachopoulos et al., 2010, Ooi et al., 2019, Wacharachaisurapol et al., 2020) were published. The main limitation of these studies was the relatively small study participant sizes. Some studies used non-compartmental analyses, thus it was not possible to identify covariates influencing PK parameters (Nakwan et al., 2016, Wacharachaisurapol et al., 2020). High interindividual variability of PK parameters have also been observed from a population pharmacokinetic study of 5 pediatric patients (Ooi et al., 2019). However, all studies highlighted that the currently recommended dose of colistin results in subtherapeutic plasma colistin concentrations when the target plasma colistin average steady-state concentration ($C_{ss,avg}$) is 2 mg/L. This target $C_{ss,avg}$ has been proposed for the treatment of MDR-GNB with a colistin MIC of ≤2 mg/L in both adults and pediatric patients (Nation et al., 2017, Ooi et al., 2019). The objectives of this study were to develop a population PK (PPK) model of intravenous colistin use in pediatric patients, identify covariates influencing PK parameters, and generate an optimized colistin dose recommendation taking into account significant covariates.

Materials and methods

Study design

This study was a prospective, multicenter, population pharmacokinetic study. Patients were recruited from two tertiary care hospitals in Bangkok, Thailand, King Chulalongkorn Memorial Hospital (KCMH), Chulalongkorn University, and the Queen Sirikit National Institute of Child Health (QSNICH), Department of Medical Services, Ministry of Public Health. Eligibility criteria for enrollment included (i) age 1 month to 12 years and (ii) suspected or proven MDR-GNB infection requiring colistin administration. Patients with a body weight of <3 kg, those receiving renal replacement therapy (RRT) or extracorporeal membrane oxygenation (ECMO) were excluded. Ethical approval to conduct the study was obtained from the Institutional Review Board of both clinical research sites. Written informed consent was obtained from parents of all patients. Written informed assent was obtained from patients aged ≥7 years if appropriate. This study was registered at the Thai Clinical Trials Registry, registration number TCTR20180526001 (http://www.clinicaltrials.in.th).

Colistin administration

Formulation of colistin injections used in this study were CMS including Mellistin™ injection (equivalent to 150 mg of CBA/vial), Siam Pharmaceutical Co. Ltd., Bangkok, Thailand (KCMH), and Colistin-150™ injection (equivalent to 150 mg of CBA/vial), Universal Medical Industry Co. Ltd., Bangkok, Thailand (QSNICH). Colistin in the form of CMS was prescribed using mg of CBA. A colistin loading dose of 4 mg of CBA/kg and a maintenance dose of 5 mg of CBA/kg/day divided into 12-h intervals with 30-min intravenous infusion per dose were suggested. However, colistin prescription decisions were ultimately decided by the attending physician.

Blood sampling

For patients between ages 1 month to 2 years, 2 (body weight <5 kg) or 3 blood samples were collected after the first dose or at steady state. For patients aged >2 years, 3 blood samples were collected after the first dose and/or at steady state. Timing for blood sample collection was 0.5–1 h, 2–4 h, 6–12 h post-dose.

Determination of colistin concentrations in plasma

Formed colistin (colistin A + colistin B) in plasma was measured at the Clinical Pharmacokinetics and Pharmacogenomics Research Unit, Department of Pharmacology, Faculty of Medicine, Chulalongkorn University by using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method as described previously (Wacharachaisurapol et al., 2020). The validated assay range of formed colistin was 0.1–6.4 mg/L. Plasma samples that exceeded colistin from the validated range were further diluted, followed by repeat determination.

Data analysis

Demographic, clinical, and microbiological data were summarized as frequencies and percentages for categorical data, and medians with interquartile ranges (IQR) for continuous data.

Population pharmacokinetic analyses and simulation

Plasma colistin concentration data were pooled from the current study and a previous study (20 patients, 7–8 plasma colistin concentrations per patient, the sampling time points: 1, 2, 4, 8, 12

(only for patients who were prescribed colistin every 12 h), 24, 48, and 72 h after initial dose) (Wacharachaisurapol et al., 2020) to form a data set for population pharmacokinetic analysis.

Software

PPK analyses and simulation were performed using Phoenix™ version 8.3. A nonlinear mixed-effects model was developed using the first-order conditional estimation-extended least-squares (FOCE ELS) method.

Base model

The population base model was parameterized in terms of clearance (CL) and volume of distribution (V). One- and two-compartment models with first-order elimination were tested in the structural model screening. The interindividual variability (IIV) was described using an exponential error model. To calculate residual variability (RV) of the parameters, the additive, proportional, and additive with proportional residual error models were tested.

Covariate model

Potential covariates were considered including age, sex, serum creatinine (SCr), estimated glomerular filtration rate (eGFR) calculated using the modified Schwartz formula (Schwartz et al., 2009), and serum albumin. Covariates were screened using a stepwise approach. During the forward addition step, covariates were added to the model. Significant covariates in this step were defined by a reduction of twice the negative log likelihood (-2LL) >6.635 ($P < 0.01$). All covariates that met the criteria were included in the full model. A backward elimination step was then done in which each covariate was sequentially removed from the full model. The covariates were retained in the final model when there was an increase of -2LL >10.828 ($P < 0.001$) during backward elimination.

Model evaluation

Goodness-of-fit plots were performed to qualify the final model. The stability of the final model was evaluated using the non-parametric bootstrap method (1000 replicates). Median values of estimated parameters with 95% confidence interval (CI) from the bootstrap method were compared with those estimated from the original dataset. A prediction-corrected visual predictive check (pcVPC) was used for internal model validation. One thousand simulation replicates of the original data set were performed with the final model. The 5th, 50th, and 95th percentiles with a 90% CI of them were calculated. The observed concentrations were then plotted against time after dose (TAD) and the observed concentrations were compared with the distribution of simulated data.

Simulation of target attainment across doses

Regarding parameter estimates from the final PPK model, a set of CL (10,000 replicates in each clinical scenario) was simulated. The IIV and RV were included in this simulation. The dosing schemes were set at 5, 7.5, 10, and 12.5 mg of CBA/kg/day divided into 12-h intervals. Each colistin dose was set as a 30-min intravenous infusion. The $C_{ss,avg}$ was calculated using simulated CL as follows,

$C_{ss,avg}$ (mg/L) = 24-h area under the curve (AUC_{24h}) (mg/L*h)/24 (h), when AUC_{24h} = dose per day (mg/kg)/CL (L/kg*h)

158 The probability of target attainment (PTA) was predicted across the target $C_{ss,avg}$ of 0.25, 0.5, 1.0,
159 2.0, and 4.0 mg/L.

Results

Patient demographics

From March 2018 to February 2021, 59 patients were enrolled (19 from KCMH, 40 from QSNICH). Data were pooled with 20 patients from a previous study (Wacharachaisurapol et al., 2020), a total of 79 patients were eligible for PPK analysis. Of these patients, 39 (49.4%) were male, median age was 2.6 years (IQR, 0.8–6.8 years); 61 (77.2%) had comorbidities; 73 (92.4%) were admitted in intensive care units (ICU). Colistin was prescribed for the treatment of ventilator-associated pneumonia (VAP) in 53 (67.1%) patients; sepsis or bloodstream infections in 24 (30.4%); and others in 8 (10.1%). Gram-negative bacteria of interest were isolated from 34 (64.2%) patients with VAP (*A. baumannii* = 27, 79.4%; Enterobacteriaceae = 5, 14.7%; *P. aeruginosa* = 2; 5.9%); 8 (33.3%) patients with sepsis or bloodstream infections (*A. baumannii* = 5; Enterobacteriaceae = 3); and 5 (62.5%) patients with other diagnoses (*A. baumannii* = 2; Enterobacteriaceae = 2; *P. aeruginosa* = 1). Carbapenem-resistant strains were 85.3%, 40%, and 1/3 of *A. baumannii,* Enterobacteriaceae (*Escherichia coli, K. pneumoniae*, and *Enterobacter* spp.), and *P. aeruginosa,* respectively. Patient demographics are summarized in Table 1.

Development of the population pharmacokinetics model

A total of 334 plasma colistin concentrations (187 from the current study; 147 from a previous study) were obtained for PPK modeling. The PK characteristics of colistin were adequately described by the one-compartment model with first-order elimination. The IIV and RV were well described by the exponential model and the proportional residual error model, respectively. For the covariate model, adding SCr and eGFR on CL significantly reduced -2LL for >6.635 in the forward addition step. However, SCr on CL (CL-SCr) resulted in the most reduction of -2LL (32.147 versus 17.805). CL-SCr was used for further addition steps. No further addition was found to reduce -2LL for >6.635. In the backward elimination step, SCr was removed from the model. It was found that -2LL increased by 32.147 (>10.828). SCr effect on CL was retained in the final model. The final PPK model was as follows:

$$V\ (L/kg) = \theta_V \times \exp(\eta_V)$$

$$CL\ (L/kg*h) = \theta_{CL} \times SCr^{\theta 1} \times \exp(\eta_{CL})$$

θ_V and θ_{CL} are the typical values of V and CL, respectively. θ_1 is the correction factor of SCr. η_V and η_{CL} are the IIV of V and CL, respectively. The details of θ_V, θ_{CL}, and θ_1 are summarized in Table 2.

Model evaluation

The goodness-of-fit plots performed for the base and final PPK model are shown in Figure 1 and 2. Compared with the base model, the final model showed no obvious bias or significant trends within the plots of individual-predicted concentrations (IPRED) (Figure 1 C) and population-predicted concentrations (PRED) (Figure 1 D) versus observed concentrations (DV), and data fitting was considerably improved. In the plots of conditional weighted residuals (CWRES) versus PRED (Figure 2 C) and TAD (Figure 2 D), the majority of concentration data were distributed around 0 and within an acceptable range of -2 to +2, which indicated no significant systematic deviations in the model fitting.

A 1000-run times bootstrap analysis was performed with no failure and demonstrated robustness of the final PPK model. The parameter estimates from the original data set were similar

to median values and within the 95% CI range of bootstrap results. A summary of the bootstrap details is shown in Table 2.

A prediction-corrected visual predictive check of plasma colistin concentrations versus TAD is shown in Figure 3. Most of the observed 5^{th}, 50^{th}, and 95^{th} quantiles distributed within the 90% CI of the predicted corresponding quantiles, indicating the precision of the final model.

Simulation of target attainment across doses

All subsequent simulations were based on the validated final model. PPK parameter estimates and variabilities were included in the simulation to create 10,000 replicates of virtual patients for each dosage regimen and SCr levels. The PTA was predicted across target $C_{ss,avg}$ of 0.25, 0.5, 1.0, 2.0, and 4.0 mg/L at the dosing schemes of 5, 7.5, 10, and 12.5 mg of CBA/kg/day divided into 12-h intervals with 30-min intravenous infusions and 5 different SCr levels. The results of PTAs are summarized in Table 3. It was demonstrated that the dose of 5 mg of CBA/kg/day recommended by the European Medicines Agency (EMA) and United States Food and Drug Administration (US FDA) would lead to an unacceptable PTAs of less than 80% across all SCr ranges in this study when the target $C_{ss,avg}$ was 2 mg/L. Patients with lower SCr require a higher dose compared with those with higher SCr. However, with a lower target $C_{ss,avg}$ of ≤1 mg/L, colistin dose of 7.5 and 5 mg of CBA/kg/day were adequate for the patients with SCr levels of 0.1–0.3 and >0.3 mg/dL, respectively.

Discussion

This study aimed to describe population pharmacokinetic parameters of formed colistin in pediatric patients and to investigate the probability of target attainment of various intravenous colistin doses to suggest the most appropriate regimen regarding significant covariates. To the best of our knowledge, this is the largest study on this issue to date. Seventy-nine patients were enrolled in the analysis. Almost all were critically ill and admitted to ICUs. Two-thirds of them were treated with colistin for ventilator-associated pneumonia and one-third for bloodstream infections. The currently recommended dose of colistin is insufficient to reach a target $C_{ss,avg}$ of 2 mg/L. Serum creatinine is a significant covariate of colistin apparent clearance. Thus, colistin in the form of CMS should be prescribed in accordance with SCr levels.

The one-compartment model with first-order elimination best describes the PK behavior of intravenous colistin in this study, which is consistent with previous PPK studies in adults (Garonzik et al., 2011, Gregoire et al., 2014, Karaiskos et al., 2015, Kristoffersson et al., 2020, Mohamed et al., 2012, Nation et al., 2017, Plachouras et al., 2009) and pediatrics (Antachopoulos et al., 2021, Ooi et al., 2019). PK parameters were estimated from the final model with good shrinkage; significant covariate was identified to lessen IIV. Many PPK studies in adults have reported that creatinine clearance (CrCl) affects the apparent CL of formed colistin (Falagas et al., 2009, Garonzik et al., 2011, Karaiskos et al., 2015, Kristoffersson et al., 2020, Nation et al., 2017) even though it is mainly eliminated by non-renal pathways. This has also been observed in a PPK study in pediatric patients (Ooi et al., 2019). This occurs due to the fact that CMS is mainly eliminated renally, and therefore accumulates in patients with decreased CrCl. The excess CMS is converted to colistin (Li et al., 2006). Blood urea nitrogen, a kidney biomarker, has also been identified as a covariate of colistin CL in one adult study (Gregoire et al., 2014). It is not surprising that SCr was identified as a significant covariate on colistin CL in this study. Although both SCr and eGFR affected colistin CL in the covariate searching process, SCr was selected and retained in the final model for statistical criteria due to it being a directly measured rather than calculated variable thus being less likely to be interfered by other factors. Unlike SCr which is measured directly in a blood sample, eGFR needs to be calculated using SCr and height or length. Measuring the height or length in critically ill pediatric patients in bed or infants and young children <2 years of age in a lying position could cause inaccurate results (Carsley et al., 2019, Rasouli et al., 2018). SCr level is correlated with body weight, and gestational age in young infants (Muhari-Stark and Burckart, 2018). Without kidney impairment, lower SCr levels may tie with younger children who have a higher volume of distribution. Although the association of age and volume of distribution could not be demonstrated in this study, it is known that younger children with a higher volume of distribution had lower plasma colistin levels (Wacharachaisurapol et al., 2020). Low SCr level may occur during pathophysiologic changes such as augmented renal clearance (ARC). ARC is found in up to 10–67% of critically ill pediatric patients (Huttner et al., 2015, van den Anker et al., 2017, Van Der Heggen et al., 2019). ARC could cause enhanced excretion of serum creatinine and drugs owing to glomerular hyperfiltration. Pediatric PPK studies report that the volume of distribution of formed colistin is related to body weight (Antachopoulos et al., 2021, Ooi et al., 2019), however, this was not observed in the current study. A possible explanation is that we used colistin dosing which was normalized by body weight in the modeling process. The plausibility of body weight on PK parameters was eliminated and made our final model simpler.

$C_{ss,avg}$ of 2 mg/L has been proposed as an initial target concentration for the bloodstream and some other infections when the colistin MIC is ≤2 mg/L (Nation et al., 2017). This target also

seems appropriate for pediatric patients (Ooi et al., 2019). The EMA and US FDA recommend a colistin dose of 2.5–5 mg of CBA/kg/day in children (European Medicines Agency, 2014, US FDA, 2017). From the simulation, 18.2–63.0% of simulated patients with a colistin dose of 5 mg of CBA/kg/day achieved the target $C_{ss,avg}$ of 2 mg/L. Ooi et al. (Ooi et al., 2019) conducted a PPK study in 5 pediatric patients with a median age of 1.75 years (range 1.25 months to 6.25 years) receiving a colistin dose of 6.6 mg of CBA/kg/day. The median $C_{ss,avg}$ was only 0.88 mg/L, with wide interindividual variability. More recently, Antachopoulos et al. (Antachopoulos et al., 2021) published a PPK study of 17 critically ill pediatric patients with a median age of 3.3 years (range 3 months to 13.75 years). The colistin doses used were 6.6 mg of CBA/kg/day in 6 patients, 9.9 mg of CBA/kg/day in 10, and 11.6 mg of CBA/kg/day in one. A wide range of the $C_{ss,avg}$ of 1.11–8.47 mg/L (median 2.92 mg/L) was observed. Only ten (58.8%) patients achieved $C_{ss,avg}$ of ≥2 mg/L. Data from the current study, together with the data from Ooi et al. and Antachopoulos et al., are evidence that the current colistin dose recommendation of 2.5–5 mg of CBA/kg/day for pediatric patients is subtherapeutic. However, almost all recommendations suggest colistin is prescribed in combination with other antibiotics (Hsu and Tamma, 2014, Nation et al., 2017). This approach might improve clinical outcomes even if the colistin level is below the desired level. *In vitro* studies demonstrated synergistic effects of carbapenems and colistin against carbapenem-resistant *A. baumannii* (meropenem + colistin) and carbapenem-resistant *K. pneumoniae* (doripenem + colistin) (Deris et al., 2012, Liu et al., 2016). A combination of doripenem and colistin at high dosage regimens also suppressed colistin-resistant and colistin-heteroresistant strains of *K. pneumoniae*. However, other antibiotics such as amikacin (if sensitive), or newer antibiotics such as cefiderocol may be preferable options when treating MDR-GNB with a colistin MIC of >2 mg/L.

A $C_{ss,avg}$ of <2 mg/L may be appropriate when the MIC of a target pathogen is <2 mg/L in bloodstream infection or <1 mg/L in lung infection. Local epidemiology and colistin MIC distribution of common MDR-GNB are crucial in guiding appropriate targets for individual institutions. Actual MIC by a proper method (such as broth microdilution) should be obtained. A dose adjustment could be considered following recommendations from this study. For example, during 2019–2020, 45 clinical isolates of *A. baumannii* from KCMH pediatric patients were obtained for colistin MIC (unpublished data). The MIC distribution was: <0.5 mg/L, 26.6%; 0.5 mg/L, 33.3%; 1 mg/L, 22.2%; 2 mg/L, 13.3%; >2 mg/L, 4.4%. An initial target $C_{ss,avg}$ of 1 mg/L would be appropriate. At this target $C_{ss,avg}$, an initial dose of 7.5 mg of CBA/kg/day may be adequate for patients with a SCr of 0.1–0.3 mg/dL while 5 mg of CBA/kg/day may be adequate for patients with higher SCr values.

Although a concern with use of higher doses of colistin is potential nephrotoxicity, in practice this is less frequently observed in pediatric patients compared to adults. Some pediatric studies report using a colistin dose of >5 mg of CBA/kg/day. Iosifidis et al. (Iosifidis et al., 2010) conducted a retrospective study of 13 pediatric patients using 19 colistin courses. High dose colistin (6.6–7.5 mg of CBA/kg/day) was prescribed in 5 courses without nephrotoxicity (nephrotoxicity definition: elevation of SCr values beyond the estimated normal range for the patient's age group). None experienced acute kidney injury in Ooi et al. (Ooi et al., 2019). One out of 17 patients in Antachopoulos et al. (Antachopoulos et al., 2021) who was administered with colistin 9.9 mg of CBA/kg/day had an elevated SCr level. However, the author concluded that kidney impairment in this patient may have occurred due to the patient's comorbidity of rapidly

progressing Burkitt lymphoma. This patient also received concomitant nephrotoxic agents (gentamicin and teicoplanin).

Our study has several strengths. It is, to our knowledge, the largest population pharmacokinetic study of intravenous colistin in pediatric patients to date. A wide range of ages of patients including infants were enrolled in the study. It has provided the first available pediatric dose suggestions of colistin regarding a significant covariate. This study also had some limitations. Firstly, because it did not include eGFR as a covariate in its model, its use in recommending dose adjustments in accordance with this parameter is limited. Secondly, the findings cannot be generalized to age groups outside the study population, especially for infants <1 month of age whom have different pharmacokinetic patterns. Thirdly, patients with severe kidney impairment or those undergoing RRT or ECMO were not included in this study, the appropriate dose for suchconditions cannot be recommended based on our study findings. Finally, the results from simulation and the relationship between pharmacokinetics and pharmacodynamics (efficacy and safety) were not explored.

The remaining research gaps that are needed for further study include (i) the efficacy and safety of higher recommended doses from simulations in children (ii) the appropriate dose of colistin for special populations such as neonates, pediatric patients with impaired kidney function, or those undergoing organ support machines (RRT, ECMO), (iii) the role of colistin therapeutic drug monitoring.

In conclusion, we successfully developed a population pharmacokinetic model of intravenous colistin in pediatric patients. Serum creatinine level is a significant covariate on colistin clearance. Simulations based on the final model revealed that the currently recommended dose of 5 mg of CBA/kg/day is subtherapeutic when the target $C_{ss,avg}$ is ≥2 mg/L. For a target $C_{ss,avg}$ of ≤1 mg/L, this dose may be adequate only for patients with SCr level of >0.3 mg/dL, and a higher dose of 7.5 mg of CBA/kg/day may be required for the patients with lower SCr levels.

Acknowledgments

The authors would like to thank all study teams including nurses at the PICU of Queen Sirikit National Institute of Child Health; nurses, pediatric residents, and pediatric infectious diseases fellows of the Department of Pediatrics, King Chulalongkorn Memorial Hospital; staff of Center of Excellence for Pediatric Infectious Diseases and Vaccines, the Faculty of Medicine, Chulalongkorn University; staff of Chula Clinical Research Laboratory (CRL)/HIV-NAT AIDS Research Laboratory; and staff of Clinical Pharmacokinetics and Pharmacogenomics Research Unit, the Faculty of Medicine, Chulalongkorn University. The authors are grateful to and acknowledge Professor Emeritus Dwip Kitayaporn; Prof. Wasee Tulvatana; Asst. Prof. Opass Putcharoen; Asst. Prof. Pajaree Chariyavilaskul; Asst. Prof. Ankanee Chanakul; all instructors of Clinical Sciences (International Program), Faculty of Medicine, Chulalongkorn University; and Assoc. Prof. Preecha Montakantikul, the Faculty of Pharmacy, Mahidol University for their constructive and insightful comments and suggestions. We also would like to acknowledge Wipaporn Natalie Songtaweesin, MD for her English editing.

Funding: This study was supported by the Ratchadaphiseksomphot Fund, Faculty of Medicine, Chulalongkorn University (Bangkok, Thailand) [grant nos. RA 57/073 and RA (MF) 09/61], and Chulalongkorn University Government Budget [grant nos. GBA_61_012_30_08 and GB-CU-61-16-30-06]. Noppadol Wacharachaisurapol is supported by a scholarship from The 100th Anniversary Chulalongkorn University Fund for Doctoral Scholarship and The 90th Anniversary Chulalongkorn University Fund (Ratchadaphiseksomphot Endowment Fund).

Competing interests: All authors declare no conflicts of interest for this manuscript.

Ethical approval: This study was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University (IRB no. 042/61) and the Research Ethics Committee, Queen Sirikit National Institute of Child Health (REC.038/2562).

Author contributions

NW: conception and design of the study (led), acquisition of data (KCMH) (led), analyses and interpretation of the data (led), population pharmacokinetic analyses and simulation (led), drafting of the article (led), revision of the article (led).

WS: Plasma colistin determination (led)

OA: study coordination, acquisition of data (KCMH) (supported).

PS: acquisition of data (QSNICH) (supported), revision of the article (supported).

SS: Study coordination, acquisition of data (QSNICH) (led).

PC: population pharmacokinetic analyses and simulation (supported).

WPV: acquisition of data (QSNICH) (supported), revision of the article (supported).

TW: conception and design of study (supported), population pharmacokinetic analyses and simulation (led), drafting of article (supported), revision of the article (supported).

TP: conception and design of the study (led), analysis and interpretation of data (supported), drafting of article (led), revision of the article (led).

All authors approved the final version for submission.

373 **References**

374 Antachopoulos C, Geladari A, Landersdorfer CB, Volakli E, Ilia S, Gikas E, et al. Population
375 pharmacokinetics and outcomes of critically ill pediatric patients treated with intravenous colistin at
376 higher than recommended doses. Antimicrob Agents Chemother 2021.
377 Antachopoulos C, Karvanen M, Iosifidis E, Jansson B, Plachouras D, Cars O, et al. Serum and
378 cerebrospinal fluid levels of colistin in pediatric patients. Antimicrob Agents Chemother
379 2010;54(9):3985-7.
380 Carsley S, Parkin PC, Tu K, Pullenayegum E, Persaud N, Maguire JL, et al. Reliability of routinely
381 collected anthropometric measurements in primary care. BMC Med Res Methodol 2019;19(1):84.
382 Deris ZZ, Yu HH, Davis K, Soon RL, Jacob J, Ku CK, et al. The combination of colistin and doripenem
383 is synergistic against Klebsiella pneumoniae at multiple inocula and suppresses colistin resistance in
384 an in vitro pharmacokinetic/pharmacodynamic model. Antimicrob Agents Chemother
385 2012;56(10):5103-12.
386 European Medicines Agency. Polymyxin Article-31 referral - Annex III amendments to relevant sections
387 of the summary of product characteristics and the package leaflets.; 2014. Available from:
388 https://www.ema.europa.eu/en/documents/referral/polymyxin-article-31-referral-annex-iii_en.pdf.
389 [Accessed 28 April 2021].
390 Falagas ME, Kasiakou SK. Use of international units when dosing colistin will help decrease confusion
391 related to various formulations of the drug around the world. Antimicrob Agents Chemother
392 2006;50(6):2274-5.
393 Falagas ME, Sideri G, Vouloumanou EK, Papadatos JH, Kafetzis DA. Intravenous colistimethate
394 (colistin) use in critically ill children without cystic fibrosis. Pediatr Infect Dis J 2009;28(2):123-7.
395 Garonzik SM, Li J, Thamlikitkul V, Paterson DL, Shoham S, Jacob J, et al. Population pharmacokinetics
396 of colistin methanesulfonate and formed colistin in critically ill patients from a multicenter study
397 provide dosing suggestions for various categories of patients. Antimicrob Agents Chemother
398 2011;55(7):3284-94.
399 Gregoire N, Mimoz O, Megarbane B, Comets E, Chatelier D, Lasocki S, et al. New colistin population
400 pharmacokinetic data in critically ill patients suggesting an alternative loading dose rationale.
401 Antimicrob Agents Chemother 2014;58(12):7324-30.
402 Hsu AJ, Tamma PD. Treatment of multidrug-resistant Gram-negative infections in children. Clin Infect
403 Dis 2014;58(10):1439-48.
404 Huttner A, Von Dach E, Renzoni A, Huttner BD, Affaticati M, Pagani L, et al. Augmented renal
405 clearance, low β-lactam concentrations and clinical outcomes in the critically ill: an observational
406 prospective cohort study. Int J Antimicrob Agents 2015;45(4):385-92.
407 Iosifidis E, Antachopoulos C, Ioannidou M, Mitroudi M, Sdougka M, Drossou-Agakidou V, et al.
408 Colistin administration to pediatric and neonatal patients. Eur J Pediatr 2010;169(7):867-74.
409 Karaiskos I, Friberg LE, Pontikis K, Ioannidis K, Tsagkari V, Galani L, et al. Colistin Population
410 Pharmacokinetics after Application of a Loading Dose of 9 MU Colistin Methanesulfonate in
411 Critically Ill Patients. Antimicrob Agents Chemother 2015;59(12):7240-8.
412 Kristoffersson AN, Rognås V, Brill MJE, Dishon-Benattar Y, Durante-Mangoni E, Daitch V, et al.
413 Population pharmacokinetics of colistin and the relation to survival in critically ill patients infected
414 with colistin susceptible and carbapenem-resistant bacteria. Clin Microbiol Infect 2020;26(12):1644-
415 50.
416 Li J, Nation RL, Turnidge JD, Milne RW, Coulthard K, Rayner CR, et al. Colistin: the re-emerging
417 antibiotic for multidrug-resistant Gram-negative bacterial infections. Lancet Infect Dis 2006;6(9):589-
418 601.
419 Liu X, Zhao M, Chen Y, Bian X, Li Y, Shi J, et al. Synergistic killing by meropenem and colistin
420 combination of carbapenem-resistant Acinetobacter baumannii isolates from Chinese patients in an in
421 vitro pharmacokinetic/pharmacodynamic model. Int J Antimicrob Agents 2016;48(5):559-63.

422 Mohamed AF, Karaiskos I, Plachouras D, Karvanen M, Pontikis K, Jansson B, et al. Application of a
423 loading dose of colistin methanesulfonate in critically ill patients: population pharmacokinetics,
424 protein binding, and prediction of bacterial kill. Antimicrob Agents Chemother 2012;56(8):4241-9.
425 Muhari-Stark E, Burckart GJ. Glomerular Filtration Rate Estimation Formulas for Pediatric and Neonatal
426 Use. J Pediatr Pharmacol Ther 2018;23(6):424-31.
427 Nakwan N, Usaha S, Chokephaibulkit K, Villani P, Regazzi M, Imberti R. Pharmacokinetics of Colistin
428 Following a Single Dose of Intravenous Colistimethate Sodium in Critically Ill Neonates. Pediatr
429 Infect Dis J 2016;35(11):1211-4.
430 Nation RL, Garonzik SM, Thamlikitkul V, Giamarellos-Bourboulis EJ, Forrest A, Paterson DL, et al.
431 Dosing guidance for intravenous colistin in critically-ill patients. Clin Infect Dis 2017;64(5):565-71.
432 National Antimicrobial Resistance Surveillance Center of Thailand (NARST). Percentage of susceptible
433 organisms isolated from blood, 79 hospitals, Jan-Jun 2020; 2021. Available from:
434 http://narst.dmsc.moph.go.th/antibiograms/2020/6/Jan-Jun2020-Blood.pdf. [Accessed 6 Apr 2021].
435 Ooi MH, Ngu SJ, Chor YK, Li J, Landersdorfer CB, Nation RL. Population Pharmacokinetics of
436 Intravenous Colistin in Pediatric Patients: Implications for the Selection of Dosage Regimens. Clin
437 Infect Dis 2019;69(11):1962-8.
438 Plachouras D, Karvanen M, Friberg LE, Papadomichelakis E, Antoniadou A, Tsangaris I, et al.
439 Population pharmacokinetic analysis of colistin methanesulfonate and colistin after intravenous
440 administration in critically ill patients with infections caused by gram-negative bacteria. Antimicrob
441 Agents Chemother 2009;53(8):3430-6.
442 Rasouli MA, Newth CJL, Khemani RG, Ross PA. Predicting Body Height in a Pediatric Intensive Care
443 Unit Using Ulnar Length. Front Pediatr 2018;6:187.
444 Schwartz GJ, Munoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, et al. New equations to estimate
445 GFR in children with CKD. J Am Soc Nephrol 2009;20(3):629-37.
446 US FDA. Coly-Mycin® M Parenteral (Colistimethate for Injection, USP); 2017. Available from:
447 https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/050108s033lbl.pdf. [Accessed 12
448 November 2020].
449 van den Anker JN, Knibbe CAJ, Tibboel D. Augmented Renal Clearance in Critically Ill Pediatric
450 Patients: Does It Impact the Outcome of Pharmacotherapy? Pediatr Crit Care Med 2017;18(9):901-2.
451 Van Der Heggen T, Dhont E, Peperstraete H, Delanghe JR, Vande Walle J, De Paepe P, et al. Augmented
452 renal clearance: a common condition in critically ill children. Pediatr Nephrol 2019;34(6):1099-106.
453 Wacharachaisurapol N, Phasomsap C, Sukkummee W, Phaisal W, Chanakul A, Wittayalertpanya S, et al.
454 Greater optimisation of pharmacokinetic/pharmacodynamic parameters through a loading dose of
455 intravenous colistin in paediatric patients. Int J Antimicrob Agents 2020;55(6):105940.
456 World Health Organization. GLOBAL PRIORITY LIST OF ANTIBIOTIC-RESISTANT BACTERIA
457 TO GUIDE RESEARCH, DISCOVERY, AND DEVELOPMENT OF NEW ANTIBIOTICS; 2017.
458 Available from: http://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-
459 ET_NM_WHO.pdf?ua=1. [Accessed 12 Nov 2019].

460

461

462 **Table 1**

463 Patient demographics.

Characteristics, N = 79	Results[a]
Age, years	2.6 (0.8–6.8)
Male sex	39 (49.4)
Weight, kg	12.0 (7.4–20.0)
Height or length, cm	90.0 (68.0–113.0)
Baseline eGFR, mL/min/1.73 m^2	147.8 (102.5–186.9)
Baseline serum creatinine, mg/dL	0.25 (0.19–0.32)
0.10–0.20	27 (34.2)
0.21–0.30	32 (40.5)
0.31–0.40	9 (11.4)
0.41–0.50	5 (6.3)
0.51–0.75	6 (7.6)
Serum albumin, g/dL	3.3 (3.1–3.6)
Comorbidities	61 (77.2)
Malignancy	23 (29.1)
Neurologic disease	14 (17.7)
Chronic cardiac disease	10 (12.7)
Chronic pulmonary disease	9 (11.4)
Receiving immunosuppressive agent(s)	7 (8.9)
Others	4 (5.1)
Intensive care unit admission	73 (92.4)
Colistin loading dose received[b]	38 (48.1)
Colistin maintenance dose, mg of CBA/kg/day	5.0 (4.9–5.0)
Colistin indication[c]	
Ventilator-associated pneumonia	53 (67.1)
Sepsis/CLABSI/CRBSI	24 (30.4)
Urinary tract infection	4 (5.1)
Skin and soft tissue/surgical site infection	3 (3.8)
Intraabdominal infection	1 (1.3)

CBA, colistin base activity; CLABSI, central line-associated bloodstream infection; CRBSI, catheter-related bloodstream infection; eGFR, estimated glomerular filtration rate.

[a] Data are shown as count (%) or median (interquartile range).

[b] Colistin methanesulfonate 4–5 mg of CBA/kg/dose.

[c] Some patients were diagnosed with >1 clinical syndromes.

464

465 **Table 2**

466 Population pharmacokinetic parameter estimates of intravenous colistin in pediatric patients and
467 bootstrap evaluation.

Parameters	Base model parameters		Final model parameters		Bootstrap (N = 1000)		
	Estimate	%RSE	Estimate	%RSE	Median	2.5^{th} percentile	97.5^{th} percentile
θ_{CL}, L/kg*h	0.137	7.99	0.069	18.40	0.069	0.048	0.097
θ_V, L/kg	0.699	7.68	0.658	6.84	0.657	0.579	0.752
θ_1	NA	NA	-0.530	-20.75	-0.533	-0.753	-0.318
Interindividual variability							
ω^2_{CL} (shrinkage)	0.449 (6.33%)	19.60	0.337 (4.81%)	20.42	0.330		
ω^2_V (shrinkage)	0.233 (22.9%)	29.16	0.301 (10.44%)	21.92	0.295		
Residual variability							
σ_{prop}	0.319	7.71	0.306	6.72	0.304	0.265	0.341

CL, clearance; RSE, relative standard error; V, volume of distribution, θ_V, typical value of V; θ_{CL}, typical value of CL; θ_1, the correction factor of serum creatinine; ω^2_V, variance of interindividual variability for V; ω^2_{CL}, variance of interindividual variability for CL; σ_{prop}, residual error for the final model.

468

469

470 **Table 3**

471 Probability of target attainment of intravenous colistin using various doses and serum creatinine
472 levels (N = 10,000 replicates per clinical scenario).

Serum creatinine (mg/dL)	Colistin dose (mg CBA/kg/day)[a]	Probability of target attainment (%)				
		Target $C_{ss,avg}$ (mg/L)				
		0.25	0.5	1.0	2.0	4.0
0.1-0.20	5	99.6	93.1	61.1	18.2	1.7
	7.5	100	98.4	83.0	42.4	8.2
	10	100	99.7	93.3	61.3	18.8
	12.5	100	99.9	97.2	75.2	30.6
0.21-0.30	5	99.9	97.1	75.0	30.1	4.0
	7.5	100	99.5	90.8	57.0	16.2
	10	100	99.9	97.0	74.9	30.7
	12.5	100	100	98.9	86.1	45.0
0.31-0.40	5	99.9	98.5	82.6	40.2	7.1
	7.5	100	99.8	94.5	66.6	23.6
	10	100	100	98.2	82.7	40.2
	12.5	100	100	99.4	91.4	56.3
0.41-0.50	5	100	99.1	88.2	49.2	10.7
	7.5	100	99.9	96.7	74.3	31.1
	10	100	100	99.0	88.3	49.1
	12.5	100	100	99.7	94.4	64.6
0.51-0.75	5	100	99.6	93.6	63.0	19.4
	7.5	100	100	98.6	84.1	44.0
	10	100	100	99.7	93.7	62.9
	12.5	100	100	99.9	97.5	76.6

CBA, colistin base activity; $C_{ss,avg}$, average plasma colistin concentration at the steady-state.
[a] Divided into 12-h intervals and 30-min intravenous infusion per dose.

473

474

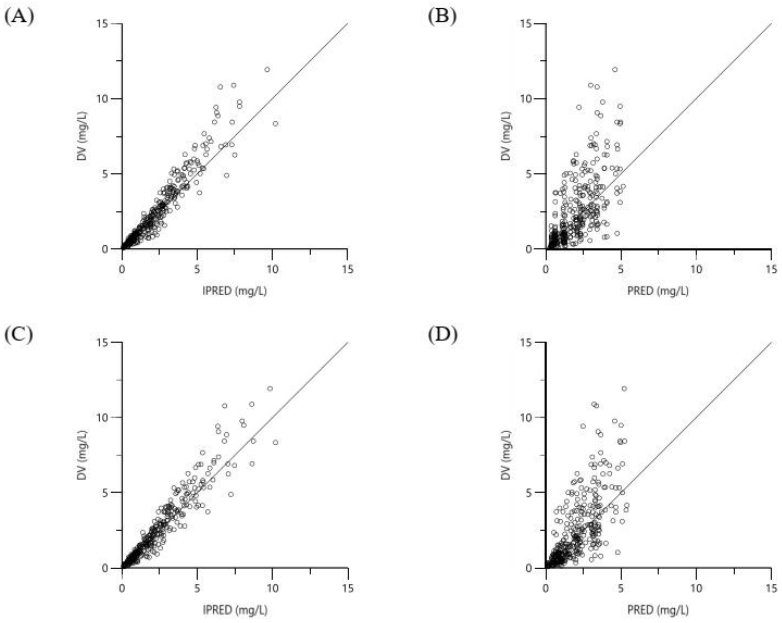


Figure 1. Goodness-of-fit plots for the base model (A and B) and the final model (C and D). (A and C) Observed concentrations (DV) versus individual-predicted concentrations (IPRED); (B and D) DV versus population-predicted concentrations (PRED).

475

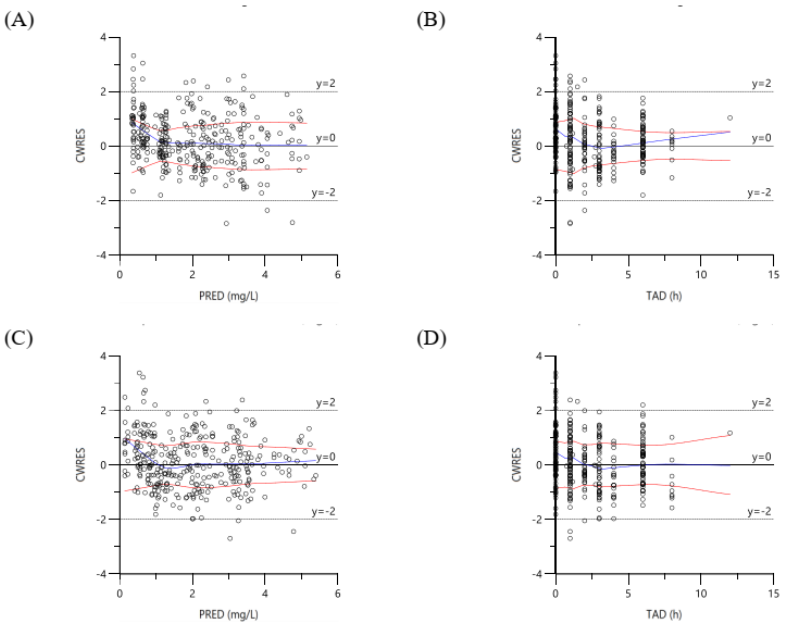


Figure 2. Goodness-of-fit plots for the base model (A and B) and the final model (C and D). (A and C) Conditional weighted residuals (CWRES) versus population-predicted concentrations (PRED); (B and D) CWRES versus time after dose (TAD). The blue line is the trend line, and the red lines are the trend lines of absolute CWRES.

476

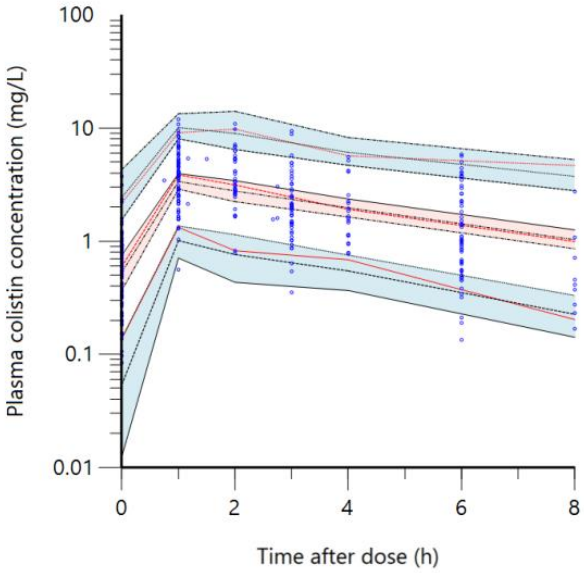


Figure 3. Prediction corrected-visual predictive check of the final model. The observed colistin concentrations are shown as blue circles. The red solid line, dashed line, and dotted line represent the 5th, 50th, and 95th percentiles of the observed concentrations; the 3 shaded areas represent the 90% confidence intervals for corresponding percentiles.

477

478

479

REFERENCES

[1] Meropol SB, Haupt AA, Debanne SM. Incidence and Outcomes of Infections Caused by Multidrug-Resistant Enterobacteriaceae in Children, 2007-2015. J Pediatric Infect Dis Soc 2017.
[2] Dhariwal AK, Tullu MS. Colistin: re-emergence of the 'forgotten' antimicrobial agent. J Postgrad Med 2013;59:208-15.
[3] World Health Organization. GLOBAL PRIORITY LIST OF ANTIBIOTIC-RESISTANT BACTERIA TO GUIDE RESEARCH, DISCOVERY, AND DEVELOPMENT OF NEW ANTIBIOTICS. 2017.
[4] National Antimicrobial Resistance Surveillance Center of Thailand (NARST). Antimicrobial resistance situation in Thailand, 2000-2020. 2021.
[5] Kapoor K, Jajoo M, Dublish S, Dabas V, Gupta S, Manchanda V. Intravenous colistin for multidrug-resistant gram-negative infections in critically ill pediatric patients. Pediatr Crit Care Med 2013;14:e268-72.
[6] Michalopoulos AS, Karatza DC. Multidrug-resistant Gram-negative infections: the use of colistin. Expert Rev Anti Infect Ther 2010;8:1009-17.
[7] Falagas ME, Kasiakou SK. Use of international units when dosing colistin will help decrease confusion related to various formulations of the drug around the world. Antimicrob Agents Chemother 2006;50:2274-5.
[8] Barnett M, Bushby SR, Wilkinson S. Sodium sulphomethyl derivatives of polymyxins. Br J Pharmacol Chemother 1964;23:552-74.
[9] Li J, Nation RL, Turnidge JD, Milne RW, Coulthard K, Rayner CR, et al. Colistin: the re-emerging antibiotic for multidrug-resistant Gram-negative bacterial infections. Lancet Infect Dis 2006;6:589-601.
[10] Falagas ME, Kasiakou SK. Colistin: the revival of polymyxins for the management of multidrug-resistant gram-negative bacterial infections. Clin Infect Dis 2005;40:1333-41.
[11] Cheah SE, Wang J, Nguyen VT, Turnidge JD, Li J, Nation RL. New pharmacokinetic/pharmacodynamic studies of systemically administered colistin against Pseudomonas aeruginosa and Acinetobacter baumannii in mouse thigh and lung infection models: smaller response in lung infection. J Antimicrob Chemother 2015;70:3291-7.
[12] Ooi MH, Ngu SJ, Chor YK, Li J, Landersdorfer CB, Nation RL. Population Pharmacokinetics of Intravenous Colistin in Pediatric Patients: Implications for the Selection of Dosage Regimens. Clin Infect Dis 2019;69:1962-8.
[13] Imberti R, Cusato M, Villani P, Carnevale L, Iotti GA, Langer M, et al. Steady-state pharmacokinetics and BAL concentration of colistin in critically Ill patients after IV colistin methanesulfonate administration. Chest 2010;138:1333-9.
[14] Antachopoulos C, Karvanen M, Iosifidis E, Jansson B, Plachouras D, Cars O, et al. Serum and cerebrospinal fluid levels of colistin in pediatric patients. Antimicrob Agents Chemother 2010;54:3985-7.
[15] Nakwan N, Usaha S, Chokephaibulkit K, Villani P, Regazzi M, Imberti R. Pharmacokinetics of Colistin Following a Single Dose of Intravenous Colistimethate Sodium in Critically Ill Neonates. Pediatr Infect Dis J 2016;35:1211-4.

[16] Couet W, Gregoire N, Gobin P, Saulnier PJ, Frasca D, Marchand S, et al. Pharmacokinetics of colistin and colistimethate sodium after a single 80-mg intravenous dose of CMS in young healthy volunteers. Clin Pharmacol Ther 2011;89:875-9.
[17] Nation RL, Garonzik SM, Thamlikitkul V, Giamarellos-Bourboulis EJ, Forrest A, Paterson DL, et al. Dosing guidance for intravenous colistin in critically-ill patients. Clin Infect Dis 2017;64:565-71.
[18] Plachouras D, Karvanen M, Friberg LE, Papadomichelakis E, Antoniadou A, Tsangaris I, et al. Population pharmacokinetic analysis of colistin methanesulfonate and colistin after intravenous administration in critically ill patients with infections caused by gram-negative bacteria. Antimicrob Agents Chemother 2009;53:3430-6.
[19] Mohamed AF, Karaiskos I, Plachouras D, Karvanen M, Pontikis K, Jansson B, et al. Application of a loading dose of colistin methanesulfonate in critically ill patients: population pharmacokinetics, protein binding, and prediction of bacterial kill. Antimicrob Agents Chemother 2012;56:4241-9.
[20] Kristoffersson AN, Rognås V, Brill MJE, Dishon-Benattar Y, Durante-Mangoni E, Daitch V, et al. Population pharmacokinetics of colistin and the relation to survival in critically ill patients infected with colistin susceptible and carbapenem-resistant bacteria. Clin Microbiol Infect 2020;26:1644-50.
[21] Garonzik SM, Li J, Thamlikitkul V, Paterson DL, Shoham S, Jacob J, et al. Population pharmacokinetics of colistin methanesulfonate and formed colistin in critically ill patients from a multicenter study provide dosing suggestions for various categories of patients. Antimicrob Agents Chemother 2011;55:3284-94.
[22] Mizuyachi K, Hara K, Wakamatsu A, Nohda S, Hirama T. Safety and pharmacokinetic evaluation of intravenous colistin methanesulfonate sodium in Japanese healthy male subjects. Curr Med Res Opin 2011;27:2261-70.
[23] Karnik ND, Sridharan K, Jadhav SP, Kadam PP, Naidu RK, Namjoshi RD, et al. Pharmacokinetics of colistin in critically ill patients with multidrug-resistant Gram-negative bacilli infection. Eur J Clin Pharmacol 2013;69:1429-36.
[24] Moni M, Sudhir AS, Dipu TS, Mohamed Z, Prabhu BP, Edathadathil F, et al. Clinical efficacy and pharmacokinetics of colistimethate sodium and colistin in critically ill patients in an Indian hospital with high endemic rates of multidrug-resistant Gram-negative bacterial infections: A prospective observational study. Int J Infect Dis 2020;100:497-506.
[25] Wacharachaisurapol N, Phasomsap C, Sukkummee W, Phaisal W, Chanakul A, Wittayalertpanya S, et al. Greater optimisation of pharmacokinetic/pharmacodynamic parameters through a loading dose of intravenous colistin in paediatric patients. Int J Antimicrob Agents 2020;55:105940.
[26] Gregoire N, Mimoz O, Megarbane B, Comets E, Chatelier D, Lasocki S, et al. New colistin population pharmacokinetic data in critically ill patients suggesting an alternative loading dose rationale. Antimicrob Agents Chemother 2014;58:7324-30.
[27] Karaiskos I, Friberg LE, Pontikis K, Ioannidis K, Tsagkari V, Galani L, et al. Colistin Population Pharmacokinetics after Application of a Loading Dose of 9 MU Colistin Methanesulfonate in Critically Ill Patients. Antimicrob Agents Chemother 2015;59:7240-8.
[28] Schwartz GJ, Munoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol 2009;20:629-37.

[29] Muhari-Stark E, Burckart GJ. Glomerular Filtration Rate Estimation Formulas for Pediatric and Neonatal Use. J Pediatr Pharmacol Ther 2018;23:424-31.
[30] Jabor A, Franeková J, Hošková L. Estimation of Glomerular Filtration Rate. In: Patel VB, Preedy VR, editors. Biomarkers in Kidney Disease. Dordrecht: Springer Netherlands; 2016. p. 1143-73.
[31] Buxton ILO. Pharmacokinetics: The Dynamics of Drug Absorption, Distribution, Metabolism, and Elimination. In: Brunton LL, Hilal-Dandan R, Knollmann BC, editors. Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 13e. New York, NY: McGraw-Hill Education; 2017.
[32] National Center for Biotechnology Information. PubChem Compound Summary for CID 5311054, Colistin. 2021.
[33] National Center for Biotechnology Information. PubChem Compound Summary for CID 70789202, Colistimethate. 2021.
[34] Lo SF. Reference Intervals for Laboratory Tests and Procedures. In: Robert M Kliegman Joseph W St Geme NJB, Samir S Shah, Robert C Tasker, Karen M Wilson, editor. Nelson Textbook of Pediatrics. 21 ed. Philadelphia, PA: Elsevier; 2020. p. e5-e14.
[35] Tracy L Sandritter BLJ, Gregory L Kearns, Jennifer A Lowry. Principles of Drug Therapy. In: Robert M Kliegman Joseph W St Geme NJB, Samir S Shah, Robert C Tasker, Karen M Wilson, editor. Nelson Textbook of Pediatrics. 21 ed. Philadelphia, PA: Elsevier; 2020. p. 445-56.
[36] Nation RL, Garonzik SM, Li J, Thamlikitkul V, Giamarellos-Bourboulis EJ, Paterson DL, et al. Updated US and European Dose Recommendations for Intravenous Colistin: How Do They Perform? Clin Infect Dis 2016;62:552-8.
[37] Chew KL, La MV, Lin RTP, Teo JWP. Colistin and Polymyxin B Susceptibility Testing for Carbapenem-Resistant and mcr-Positive Enterobacteriaceae: Comparison of Sensititre, MicroScan, Vitek 2, and Etest with Broth Microdilution. J Clin Microbiol 2017;55:2609-16.
[38] Matuschek E, Åhman J, Webster C, Kahlmeter G. Antimicrobial susceptibility testing of colistin - evaluation of seven commercial MIC products against standard broth microdilution for Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, and Acinetobacter spp. Clin Microbiol Infect 2018;24:865-70.
[39] Vasoo S. Susceptibility Testing for the Polymyxins: Two Steps Back, Three Steps Forward? J Clin Microbiol 2017;55:2573-82.
[40] US FDA. Coly-Mycin® M Parenteral (Colistimethate for Injection, USP). 2017.
[41] European Medicines Agency. Polymyxin Article-31 referral - Annex III amendments to relevant sections of the summary of product characteristics and the package leaflets. 2014.
[42] Falagas ME, Vouloumanou EK, Rafailidis PI. Systemic colistin use in children without cystic fibrosis: a systematic review of the literature. Int J Antimicrob Agents 2009;33:503.e1-.e13.
[43] Falagas ME, Sideri G, Vouloumanou EK, Papadatos JH, Kafetzis DA. Intravenous colistimethate (colistin) use in critically ill children without cystic fibrosis. Pediatr Infect Dis J 2009;28:123-7.
[44] Paksu MS, Paksu S, Karadag A, Sensoy G, Asilioglu N, Yildizdas D, et al. Old agent, new experience: colistin use in the paediatric Intensive Care Unit--a multicentre study. Int J Antimicrob Agents 2012;40:140-4.

[45] Karli A, Paksu MS, Karadag A, Belet N, Paksu S, Guney AK, et al. Colistin use in pediatric intensive care unit for severe nosocomial infections: experience of an university hospital. Ann Clin Microbiol Antimicrob 2013;12:32.
[46] Karbuz A, Ozdemir H, Yaman A, Kocabas BA, Odek C, Guriz H, et al. The use of colistin in critically ill children in a pediatric intensive care unit. Pediatr Infect Dis J 2014;33:e19-24.
[47] Sahbudak Bal Z, Kamit Can F, Yazici P, Berna Anil A, Duyu M, Yilmaz Ciftdogan D, et al. The evaluation of safety and efficacy of colistin use in pediatric intensive care unit: Results from two reference hospitals and review of literature. J Infect Chemother 2018;24:370-5.
[48] Tamma PD, Newland JG, Pannaraj PS, Metjian TA, Banerjee R, Gerber JS, et al. The use of intravenous colistin among children in the United States: results from a multicenter, case series. Pediatr Infect Dis J 2013;32:17-22.
[49] Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract 2012;120:c179-84.
[50] Miano TA, Lautenbach E, Wilson FP, Guo W, Borovskiy Y, Hennessy S. Attributable Risk and Time Course of Colistin-Associated Acute Kidney Injury. Clin J Am Soc Nephrol 2018;13:542-50.
[51] Rattanaumpawan P, Ungprasert P, Thamlikitkul V. Risk factors for colistin-associated nephrotoxicity. J Infect 2011;62:187-90.
[52] Horcajada JP, Sorlí L, Luque S, Benito N, Segura C, Campillo N, et al. Validation of a colistin plasma concentration breakpoint as a predictor of nephrotoxicity in patients treated with colistin methanesulfonate. Int J Antimicrob Agents 2016;48:725-7.
[53] İşgüder R, Ağın H, Ceylan G, Bayram N, Devrim İ. Safety and efficacy of intravenous colistin use for the treatment of nosocomial multidrug-resistant Acinetobacter baumannii infections in a pediatric intensive care unit. Am J Infect Control 2016;44:734-5.
[54] Iosifidis E, Antachopoulos C, Ioannidou M, Mitroudi M, Sdougka M, Drossou-Agakidou V, et al. Colistin administration to pediatric and neonatal patients. Eur J Pediatr 2010;169:867-74.
[55] Ozsurekci Y, Aykac K, Cengiz AB, Bayhan C, Sancak B, Karadag Oncel E, et al. Is colistin effective in the treatment of infections caused by multidrug-resistant (MDR) or extremely drug-resistant (XDR) gram-negative microorganisms in children? Diagn Microbiol Infect Dis 2016;85:233-8.
[56] Li J, Milne RW, Nation RL, Turnidge JD, Coulthard K. Stability of colistin and colistin methanesulfonate in aqueous media and plasma as determined by high-performance liquid chromatography. Antimicrob Agents Chemother 2003;47:1364-70.
[57] Li J, Milne RW, Nation RL, Turnidge JD, Coulthard K, Valentine J. Simple method for assaying colistin methanesulfonate in plasma and urine using high-performance liquid chromatography. Antimicrob Agents Chemother 2002;46:3304-7.
[58] Reed MD, Stern RC, O'Riordan MA, Blumer JL. The pharmacokinetics of colistin in patients with cystic fibrosis. J Clin Pharmacol 2001;41:645-54.
[59] Poole CF. Chapter 2 - Derivatization in liquid chromatography. In: Fanali S, Haddad PR, Poole CF, Riekkola M-L, editors. Liquid Chromatography (Second Edition): Elsevier; 2017. p. 39-68.
[60] Li J, Milne RW, Nation RL, Turnidge JD, Coulthard K, Johnson DW. A simple method for the assay of colistin in human plasma, using pre-column derivatization with

9-fluorenylmethyl chloroformate in solid-phase extraction cartridges and reversed-phase high-performance liquid chromatography. J Chromatogr B Biomed Sci Appl 2001;761:167-75.
[61] Ette EI, Williams PJ. Population pharmacokinetics I: background, concepts, and models. Ann Pharmacother 2004;38:1702-6.
[62] Charles B. Population pharmacokinetics: an overview. Aust Prescr 2014;37:210-3.
[63] Ezzet F, Pinheiro JC. Linear, Generalized Linear, and Nonlinear Mixed Effects Models. Pharmacometrics2007. p. 103-35.
[64] Ette EI, Williams PJ, Ahmad A. Population Pharmacokinetic Estimation Methods. Pharmacometrics2007. p. 263-85.
[65] Williams PJ, Kim YH, Ette EI. The Epistemology of Pharmacometrics. Pharmacometrics2007. p. 223-44.
[66] Bonate PL. Nonlinear Mixed Effects Models: Theory. Pharmacokinetic-Pharmacodynamic Modeling and Simulation. Boston, MA: Springer US; 2011. p. 233-301.
[67] Bergstrand M, Hooker AC, Wallin JE, Karlsson MO. Prediction-corrected visual predictive checks for diagnosing nonlinear mixed-effects models. Aaps j 2011;13:143-51.
[68] Butterfield J, Lodise TP, Pai MP. Chapter 9 - Applications of Pharmacokinetic and Pharmacodynamic Principles to Optimize Drug Dosage Selection: Example of Antibiotic Therapy Management. In: Dasgupta A, editor. Therapeutic Drug Monitoring. Boston: Academic Press; 2012. p. 175-96.
[69] Bonate PL. Clinical Trial Simulation: Theory. Pharmacometrics2007. p. 851-71.
[70] Ette EI, Williams PJ, Lane JR. Population pharmacokinetics III: design, analysis, and application of population pharmacokinetic Studies. Ann Pharmacother 2004;38:2136-44.
[71] Gobin P, Lemaitre F, Marchand S, Couet W, Olivier JC. Assay of colistin and colistin methanesulfonate in plasma and urine by liquid chromatography-tandem mass spectrometry. Antimicrob Agents Chemother 2010;54:1941-8.
[72] Dotsikas Y, Markopoulou CK, Koundourellis JE, Loukas YL. Validation of a novel LC-MS/MS method for the quantitation of colistin A and B in human plasma. J Sep Sci 2011;34:37-45.
[73] Antachopoulos C, Geladari A, Landersdorfer CB, Volakli E, Ilia S, Gikas E, et al. Population pharmacokinetics and outcomes of critically ill pediatric patients treated with intravenous colistin at higher than recommended doses. Antimicrob Agents Chemother 2021.
[74] Rasouli MA, Newth CJL, Khemani RG, Ross PA. Predicting Body Height in a Pediatric Intensive Care Unit Using Ulnar Length. Front Pediatr 2018;6:187.
[75] Carsley S, Parkin PC, Tu K, Pullenayegum E, Persaud N, Maguire JL, et al. Reliability of routinely collected anthropometric measurements in primary care. BMC Med Res Methodol 2019;19:84.
[76] Huttner A, Von Dach E, Renzoni A, Huttner BD, Affaticati M, Pagani L, et al. Augmented renal clearance, low β-lactam concentrations and clinical outcomes in the critically ill: an observational prospective cohort study. Int J Antimicrob Agents 2015;45:385-92.

[77] van den Anker JN, Knibbe CAJ, Tibboel D. Augmented Renal Clearance in Critically Ill Pediatric Patients: Does It Impact the Outcome of Pharmacotherapy? Pediatr Crit Care Med 2017;18:901-2.
[78] Van Der Heggen T, Dhont E, Peperstraete H, Delanghe JR, Vande Walle J, De Paepe P, et al. Augmented renal clearance: a common condition in critically ill children. Pediatr Nephrol 2019;34:1099-106.
[79] Hsu AJ, Tamma PD. Treatment of multidrug-resistant Gram-negative infections in children. Clin Infect Dis 2014;58:1439-48.
[80] Wacharachaisurapol N, Kawichai S, Chanakul A, Puthanakit T. No increased acute kidney injury rate through giving an intravenous colistin loading dose in pediatric patients. Int J Infect Dis 2021;106:91-7.
[81] Liu X, Zhao M, Chen Y, Bian X, Li Y, Shi J, et al. Synergistic killing by meropenem and colistin combination of carbapenem-resistant Acinetobacter baumannii isolates from Chinese patients in an in vitro pharmacokinetic/pharmacodynamic model. Int J Antimicrob Agents 2016;48:559-63.
[82] Deris ZZ, Yu HH, Davis K, Soon RL, Jacob J, Ku CK, et al. The combination of colistin and doripenem is synergistic against Klebsiella pneumoniae at multiple inocula and suppresses colistin resistance in an in vitro pharmacokinetic/pharmacodynamic model. Antimicrob Agents Chemother 2012;56:5103-12.
[83] Blot SI, Pea F, Lipman J. The effect of pathophysiology on pharmacokinetics in the critically ill patient--concepts appraised by the example of antimicrobial agents. Adv Drug Deliv Rev 2014;77:3-11.
[84] Tsuji BT, Pogue JM, Zavascki AP, Paul M, Daikos GL, Forrest A, et al. International Consensus Guidelines for the Optimal Use of the Polymyxins: Endorsed by the American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Society of America (IDSA), International Society for Anti-infective Pharmacology (ISAP), Society of Critical Care Medicine (SCCM), and Society of Infectious Diseases Pharmacists (SIDP). Pharmacotherapy 2019;39:10-39.
[85] Karageorgos SA, Bassiri H, Siakallis G, Miligkos M, Tsioutis C. Intravenous colistin use for infections due to MDR Gram-negative bacilli in critically ill paediatric patients: a systematic review and meta-analysis. J Antimicrob Chemother 2019;74:2497-506.
[86] U.S. Department of Health and Human Services Food and Drug Administration. Bioanalytical Method Validation Guidance for Industry. 2018.

VITA

NAME Noppadol Wacharachaisurapol

DATE OF BIRTH 12 November 1979

PLACE OF BIRTH

INSTITUTIONS ATTENDED
- Diploma of the Thai Subspecialty Board of Pediatric Infectious Diseases, KCMH, Faculty of Medicine, Chulalongkorn University, Thailand
- Diploma of the Thai Board of Pediatrics, KCMH, Faculty of Medicine, Chulalongkorn University, Thailand
- Doctor of Medicine (First Class Honor), Faculty of Medicine, Chulalongkorn University, Thailand
- Bachelor of Science in Pharmacy, Faculty of Pharmacy, Mahidol University, Thailand

HOME ADDRESS

PUBLICATION

1.Wiriyakosol S, Kongdan Y, Euanorasetr C, Wacharachaisurapol N, Lertsithichai P. Randomized controlled trial of bisacodyl suppository versus placebo for postoperative ileus after elective colectomy for colon cancer. Asian J Surg. 2007 Jul;30(3):167-72. doi: 10.1016/S1015-9584(08)60017-2. PMID: 17638634.

2. Wacharachaisurapol N, Bender JM, Wang L, Bliss D, Ponrartana S, Pannaraj PS. Abdominal Actinomycosis in Children: A Case Report and Literature Review. Pediatr Infect Dis J. 2017 Mar;36(3):e76-e79. doi: 10.1097/INF.0000000000001416. PMID: 27870811; PMCID: PMC5303171.

3. Suchartlikitwong P, Anugulruengkitt S, Wacharachaisurapol N, Jantarabenjakul W, Sophonphan J, Theerawit T, Chatsuwan T, Wattanavijitkul T, Puthanakit T. Optimizing Vancomycin Use Through 2-Point AUC-Based Therapeutic Drug Monitoring in Pediatric Patients. J Clin Pharmacol. 2019 Dec;59(12):1597-1605. doi: 10.1002/jcph.1498. Epub 2019 Jul 24. PMID: 31342543.

4. Janewongwirot P, Jantarabenjakul W, Anugulruengkitt S, Anunsittichai O, Saengseesom W, Buranapraditkun S, Sophonphan J, Wacharachaisurapol N, Jitrungruengnij N, Pancharoen C, Puthanakit T. A randomized open-label trial of 2-dose or 3-dose pre-exposure rabies prophylaxis among Thai children. Vaccine. 2019 Aug 23;37(36):5307-5313. doi: 10.1016/j.vaccine.2019.07.055. Epub 2019 Jul 26. PMID: 31358408.

5. Wacharachaisurapol N, Phasomsap C, Sukkummee W, Phaisal W, Chanakul A, Wittayalertpanya S, Chariyavilaskul P, Puthanakit T. Greater optimisation of pharmacokinetic/pharmacodynamic parameters through a loading dose of intravenous colistin in paediatric patients. Int J Antimicrob Agents. 2020 Jun;55(6):105940. doi: 10.1016/j.ijantimicag.2020.105940. Epub 2020 Mar 13. PMID: 32179149.

6. Jitrungruengnij N, Anugulruengkitt S, Rattananupong T, Prinyawat M, Jantarabenjakul W, Wacharachaisurapol N, Chatsuwan T, Janewongwirot P, Suchartlikitwong P, Tawan M, Kanchanabutr P, Pancharoen C, Puthanakit T. Efficacy of chlorhexidine patches on central line-associated bloodstream infections in children. Pediatr Int.

2020 Jul;62(7):789-796. doi: 10.1111/ped.14200. Epub 2020 Jul 9. PMID: 32065485.
7. Aikphaibul P, Theerawit T, Sophonphan J, Wacharachaisurapol N, Jitrungruengnij N, Puthanakit T. Risk factors of severe hospitalized respiratory syncytial virus infection in tertiary care center in Thailand. Influenza Other Respir Viruses. 2021 Jan;15(1):64-71. doi: 10.1111/irv.12793. Epub 2020 Aug 12. PMID: 32783380; PMCID: PMC7767956.
8. Songtaweesin WN, Kawichai S, Phanuphak N, Cressey TR, Wongharn P, Saisaengjan C, Chinbunchorn T, Janyam S, Linjongrat D, Puthanakit T; CE-PID - TRC Adolescent Study Team. Youth-friendly services and a mobile phone application to promote adherence to pre-exposure prophylaxis among adolescent men who have sex with men and transgender women at-risk for HIV in Thailand: a randomized control trial. J Int AIDS Soc. 2020 Sep;23 Suppl 5(Suppl 5):e25564. doi: 10.1002/jia2.25564. PMID: 32869511; PMCID: PMC7459171.
9. Wacharachaisurapol N, Jitrungruengnij N, Janewongwirot P, Suchartlikitwong P, Chautrakarn S, Jantarabenjakul W, Anugulruengkitt S, Theerawit T, Sophonphan J, Deerojanawong J, Pancharoen C, Puthanakit T. High prescribing rates of third-generation cephalosporins in children hospitalized with acute lower respiratory infections at a university hospital. Int J Infect Dis. 2021 Jan;102:369-374. doi: 10.1016/j.ijid.2020.10.105. Epub 2020 Nov 10. PMID: 33186703.
10. Rungsitsathian K, Wacharachaisurapol N, Nakaranurack C, Usayaporn S, Sakares W, Kawichai S, Jantarabenjakul W, Puthanakit T, Anugulruengkitt S. Acceptance and Outcome of Interventions in Meropenem De-escalation ASP in Pediatrics. Pediatr Int. 2021 Mar 19. doi: 10.1111/ped.14703. Epub ahead of print. PMID: 33740838.
11. Wacharachaisurapol N, Kawichai S, Chanakul A, Puthanakit T. No increased acute kidney injury rate through giving an intravenous colistin loading dose in pediatric patients. Int J Infect Dis. 2021 Mar 23;106:91-97. doi: 10.1016/j.ijid.2021.03.059. Epub ahead of print. PMID: 33771669.

AWARD RECEIVED

- The winner prize PIDST Poster Presentation Award of the 23rd Annual Meeting of Pediatric Infectious Disease Society of Thailand
- The 2nd prize PIDST Oral Presentation Award of the 22nd Annual Meeting of Pediatric Infectious Disease Society of Thailand
- The winner award for resident research contest for the 81st Thai Congress of Pediatrics of the Royal College of Pediatricians of Thailand and Pediatric Society of Thailand
- Pediatric International Scholarship Award of the Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Thailand
- Health System Research Institute
- Ratchadaphiseksomphot Fund, Faculty of Medicine, Chulalongkorn University
- Chulalongkorn University Government Budget “The 100th Anniversary Chulalongkorn University Fund for Doctoral Scholarship” and “The 90th Anniversary Chulalongkorn University Fund (Ratchadaphiseksomphot Endowment Fund)”