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Original Article

Population pharmacokinetics of colistin and the relation to survival in critically ill patients infected with colistin susceptible and carbapenem-resistant bacteria☆

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ABSTRACT

Objectives: The aim was to analyse the population pharmacokinetics of colistin and to explore the relationship between colistin exposure and time to death.
Methods: Patients included in the AIDA randomized controlled trial were treated with colistin for severe infections caused by carbapenem-resistant Gram-negative bacteria. All subjects received a 9 million units (MU) loading dose, followed by a 4.5 MU twice daily maintenance dose, with dose reduction if creatinine clearance (CrCL) < 50 mL/min. Individual colistin exposures were estimated from the developed population pharmacokinetic model and an optimized two-sample per patient sampling design. Time to death was evaluated in a parametric survival analysis.
Results: Out of 406 randomized patients, 349 contributed pharmacokinetic data. The median (90% range) colistin plasma concentration was 0.44 (0.14–1.59) mg/L at 15 minutes after the end of first infusion. In samples drawn 10 hr after a maintenance dose, concentrations were >2 mg/L in 94% (195/208) and 44% (38/87) of patients with CrCL ≤120 mL/min, and >120 mL/min, respectively. Colistin methanesulfonate sodium (CMS) and colistin clearances were strongly dependent on CrCL. High colistin exposure to MIC ratio was associated with increased hazard of death in the multivariate analysis (adjusted hazard ratio (95% CI): 1.07 (1.03–1.12)). Other significant predictors included SOFA score at baseline (HR 1.24 (1.19–1.30) per score increase), age and *Acinetobacter* or *Pseudomonas* as index pathogen.
Discussion: The population pharmacokinetic model predicted that >90% of the patients had colistin concentrations >2 mg/L at steady state, but only 66% at 4 hr after start of treatment. High colistin

☆ This work is dedicated to Johan Mouton, coordinator of the AIDA project.

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exposure was associated with poor kidney function, and was not related to a prolonged survival.
A.N. Kristoffersson, Clin Microbiol Infect 2020;▪:1

Introduction

The currently recommended European Medicines Agency dosing regimens for colistin are based on few data [1]. Moreover, it is not well understood if the high variability in colistin exposures observed between patients is related to the treatment outcome. The EU-funded (FP7) AIDA project was designed to elucidate clinical effectiveness for old off-label antibiotics seeing resurgent use due to increasing emergence of drug resistance [2]. One of the studies, a multicentre, open-label, randomized controlled clinical trial, was designed to clarify the clinical value of adding meropenem to colistin treatment in patients with severe infections caused by carbapenem-resistant bacteria, as earlier demonstrated *in vitro* [3]. The trial showed no statistically significant difference between treatment arms in the primary endpoint success/failure, or of survival, at 14 or 28 days after randomization [4].

A secondary aim of the study was to further characterize the population pharmacokinetics (PK) of colistin to better understand differences between patients and relate individual exposures to clinical outcome measures. Colistin is administered as the inactive prodrug colistin methanesulfonate sodium (CMS), and to more rapidly achieve colistin concentrations believed to be therapeutic, a loading dose of 9 million units (MU) of CMS has been recommended [1]. In addition to high inter-individual variability (IIV), CMS and colistin show a high inter-occasion (day-to-day) variability (IOV) [5–7]. Creatinine clearance (CrCL) has been suggested to explain some of the variability [7,8], but further quantification of covariate relationships is needed to improve individualization of CMS/colistin dosing. For example, patients with CrCL >80 mL/min may be underexposed based on targets defined in preclinical studies [9]. Moreover, the clinical exposure–response relationship needs to be better understood to motivate dose adjustments, given that CMS/colistin is nephrotoxic. To this end, the AIDA study provided a good basis to explore how colistin PK is related to clinical outcomes, with population PK modelling, where information is 'borrowed' between individuals and the number of PK samples per subject can be reduced to limit the logistic footprint and cost [10].

The objective of the current analysis was to characterize the population PK in the AIDA study of critically ill patients and define any significant covariate relationships for colistin and CMS. To this end, a sparse PK sampling design was identified through optimal design methodology, which focused on characterizing the individual colistin exposure. Moreover, we explored if patient variability in colistin exposure was related to survival time in a parametric time-to-event analysis. Such an analysis is more informative than a logistic regression analysis, e.g. survival at day 14 or 28.

Patients and methods

Patients and dosing

The study was conducted according to the principles expressed in the Declaration of Helsinki. All participating hospitals obtained ethics approval from their respective ethics committees. Informed consent was obtained from each eligible patient or the patient's representative. Adults with severe infections caused by carbapenem-non-susceptible (MIC >2 mg/L) Gram-negative bacteria that were susceptible to colistin by E-test or Vitek-2 (Biomerieux) and EUCAST susceptibility criteria at the time of inclusion (MIC ≤2 mg/L for *Acinetobacter baumannii* and Enterobacterales and ≤4 mg/L for *Pseudomonas aeruginosa*) were eligible [2,4]. Patient demographics have been described earlier [4]. MICs were redone in a central laboratory using standard microdilution [11].

A colistin loading dose of 9 MU of CMS (300 mg of colistin base activity, CBA) was administered to all patients after randomization, independent of their CrCL value, as long as they had been on colistin treatment for <48 hr but had not yet received a loading dose (maximum CMS dose of 13.5 MU during 24 hr). The maintenance CMS dose was 4.5 MU (150 mg of CBA) every 12 hr for patients with CrCL ≥50 mL/min, while for patients with CrCL <50 mL/min (without renal replacement therapy, RRT), the total daily maintenance dose was adjusted to $2 \times (1.5 \times \text{CrCL} + 30)/30$ MU [8]. Patients with continuous RRT received a dose of 6 MU every 12 hr and patients with intermittent haemodialysis received 1 MU every 12 hr and 1 MU of supplemental dose after dialysis. All CMS doses were administered as 30-minute infusions immediately after preparation of the solution.

Population pharmacokinetic modelling

Two blood samples per patient, at 45 minutes and 10 hr after the start of infusions on different dosing occasions (times defined by optimal design [12]), were assayed for CMS and colistin (please see supplementary material). The most recent model by Karaiskos et al. [13] formed the basis for the population PK analysis. Covariates were explored for their relationship to the parameters. Patients on RRT were not included in the model building, but their individual exposures were predicted after adding RRT parameters [13].

Exposure–response analysis

The outcome assessed in the exposure–response analysis was time to death, with censoring at 28 days after randomization. Various distributions were first explored to describe the event data. Thereafter a multivariate analysis of potential predictors was performed which included demographics and variables related to patient status, infection and treatment (please see supplementary material).

Results

Observed CMS and colistin concentrations

A total of 644 CMS concentrations and 645 colistin concentrations from 349 patients were included in the PK analysis. For 57 of the 406 patients, no concentration measurements were available (please see supplementary material). For 48% of the patients (166/349), both PK samples were collected within the first 24 hr after their very first CMS dose. The median (90% range) concentration in the 45-minute sample from these patients was 29.7 (9.8–63.9) mg/L for CMS and 0.44 (0.14–1.59) mg/L for colistin (Fig. 1).

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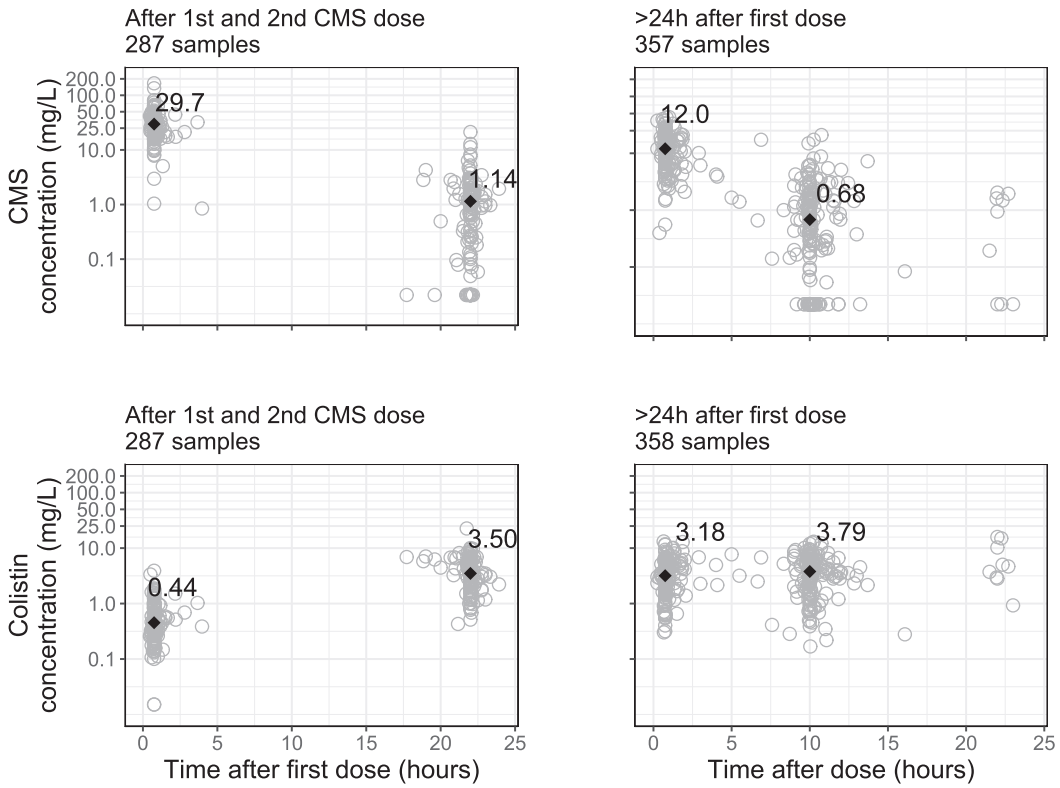

Fig. 1. Observed CMS and colistin concentrations. Median values (black) for the first (0–7 hr after dose) and second (7–13 hr after dose) sample (in total 1289 concentrations from 349 patients) are illustrated. The nominal sampling times were 45 minutes and 10 hr after start of an infusion. The left panels show concentrations drawn within 24 hr after the first (loading) dose, while the right panels show concentrations drawn after a later dose. The sample with the lowest CMS concentration at 45 minutes had also the lowest colistin concentration.

Colistin concentrations determined 10 hr after a maintenance dose were lower in patients with higher CrCL values (n = 295, Fig. 2). Patients with CrCL <50 mL/min, who had received an adjusted maintenance dose, had similar concentrations as patients with CrCL of 50–80 mL/min. The median (90% range) colistin concentrations at this time point was 5.4 (3.0–10.9), 4.6 (2.2–7.7),

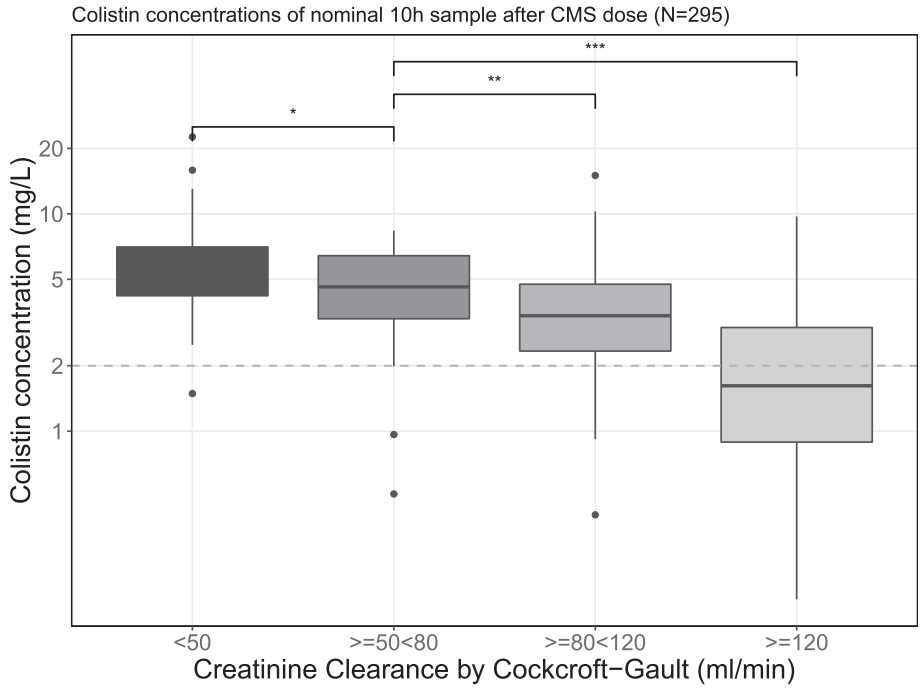

Fig. 2. Colistin concentrations at 10 hr after a maintenance dose versus creatinine clearance as computed by the Cockcroft–Gault equation. The number of patients per group was 94, 62, 52 and 87, respectively. Mann–Whitney U test (NS, non-significant; *p <0.05; **p >0.01; ***p > 0.001, using R package ggsignif).

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3.4 (1.1–8.0) and 1.6 (0.4–4.8) mg/L for CrCL of <50 ($n = 94$), 50–79 ($n = 62$), 80–119 ($n = 52$) and ≥120 ($n = 87$) mL/min. In the CrCL intervals of 50–79, 80–119 and ≥ 120 mL/min, where all patients received the same dose, 95% (59/62), 83% (43/52) and 44% (38/87) of the patients had a measured colistin concentration >2 mg/L, and 58% (36/62), 37% (19/52) and 11% (10/87) had a concentration >4 mg/L, in their 10-hr sample. There was no apparent change in measured CMS or colistin exposures over the 3.5 years the trial was conducted.

Population pharmacokinetic modelling

The final model (Fig. S1) demonstrates a good description of both typical trends and variability of the collected CMS and colistin concentrations (Fig. S2). CrCL based on the Cockcroft–Gault formula was the only included covariate but was found to be significant ($p < 0.001$) for both CMS clearance and apparent colistin clearance, and decreased variability from 45% to 13% (CMS clearance) and 36% to 24% (colistin clearance) (Table S1). Modification of Diet in Renal Disease (MDRD), in combination with body weight, resulted in worse description of the data than CrCL alone and was therefore not selected. In the final model, the typical colistin half-lives were estimated to 25, 17 and 12 hr, for patients with CrCL of 50, 80 and 120 mL/min, respectively.

The model predicts that for the dose regimen used here (9 MU load + 4.5 MU every 12 hr maintenance dose), a typical patient with CrCL of 50, 80, 120 and 180 mL/min will have an average colistin concentration during the first 120 hr of 6.4, 4.4, 3.0 and 1.8 mg/L, respectively (Fig. 3). The corresponding predicted percentages of patients with average concentrations >2 and > 4 mg/L are 100%, 100%, 97% and 30% and 99%, 69%, 5.4% and 0%, respectively. The patients' predicted colistin $fAUC_{24h}$/MIC was 0.2–169 (median of 25), for a free fraction of 34% (determined in plasma from critically ill patients and a colistin A to colistin B ratio similar to the clinically available CMS product [7]).

Exposure–survival analysis

The time-to-death analysis included all 406 patients. The events were best described by a generalized log-logistic distribution [14], suggesting a peak in the hazard of death on day 4 after randomization. Univariate analysis results of evaluated predictors are presented in Table S2. Multivariate analysis (Table 1) resulted in the following four significant predictors, included in the order mentioned (HR > 1 associated with increased risk of fatality): (a) SOFA score at randomization ($p < 0.001$, adjusted HR 1.20 (1.15–1.25)), (b) age of the subject ($p < 0.001$, adjusted HR 1.02 (1.01–1.03)), (c) the infecting pathogen not being *Acinetobacter* or *Pseudomonas aeruginosa* ($p < 0.01$, adjusted HR 0.49 (0.33–0.83)) and (d) the ratio between average colistin concentrations over 5 days ($C_{avg,120h}$) and colistin MIC ($p < 0.001$, adjusted HR 1.07 (1.03–1.12)). Variables of renal function (Table S2) were not better predictors than $C_{avg,120h}/MIC_{colistin}$. Neither was an interaction between CrCL and $C_{avg,120h}/MIC_{colistin}$ significant. The same four predictors were identified when subjects on RRT ($n = 38$) were excluded from the analysis. When subjects without PK samples or centrally determined MICs ($n = 112$) were excluded from the analysis, pathogen type was no longer significant. Simulations from the final parametric time-to-death model captured the observed data and the trends of the included predictors (Fig. 4).

Discussion

This population PK analysis of CMS and colistin included 349 patients (319 patients not on RRT) and is, to our knowledge, the largest patient cohort studied up to date regarding CMS and colistin PK. Included patients had a large spread in renal function (median CrCL of 70 mL/min (IQR 38–137 mL/min, range 9–658 mL/min) for non-RRT patients) and both CMS and colistin clearances were highly correlated to CrCL. The applied dosing regimen of a 9 MU loading dose followed by a 4.5 MU every 12 hr maintenance dose resulted in colistin concentrations above the suggested PK/PD target [9] and the current EUCAST breakpoint of 2 mg/L for the majority of the studied patients, at 22 hr after start of colistin treatment. Surprisingly, the colistin concentration over MIC ratio was not associated with survival, but rather with hazard of fatality.

At 45 minutes after the start of the loading dose infusion, the measured colistin concentration was low (median 0.44 mg/L), which illustrates that the conversion of CMS to colistin was not immediate in these patients. At 4 hr, 66% of the patients had predicted colistin

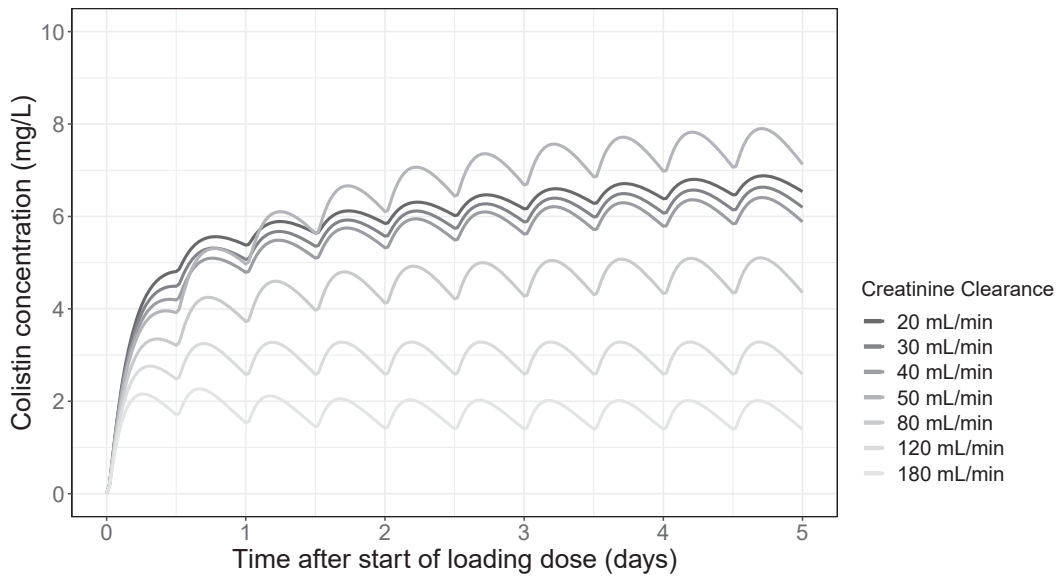

Fig. 3. Predicted total colistin concentrations from the developed model for a range of CrCL values. The same dosing formula as in the AIDA study was applied where patients with creatinine clearance <50 mL/min received an adjusted maintenance dose.

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Table 1
Parameter estimates of the final time-to-event model (406 patients) from the multivariate analysis

Model parameter (unit)	Explanation of model parameter	Estimate, relative standard error (%)	Hazard ratio (95% CI)
p	Shape parameter	2.43 (20)	—
λ	Scale parameter	0.119 (11)	—
γ	Scale parameter	0.298 (16)	—
θ_1 (-)	SOFA score at randomization (per point)[a]	0.181 (12)	1.20 (1.15–1.25)
θ_2 (year^{-1})	Age (per year)[a]	0.022 (25)	1.02 (1.01–1.03)
θ_3 (-)	Index isolate other than *Acinetobacter* or *Pseudomonas*[a]	−0.650 (36)	0.49 (0.33–0.83)
θ_4 (-)	$C_{avg,120h}/MIC_{colistin}$[a]	0.072 (27)	1.07 (1.03–1.12)

The relative standard error is a measure of how well estimated the parameter is. Base hazard function: $h_0(t) = \frac{\lambda p(\lambda t)^{p-1}}{(1+(\gamma t)^p)}$ where p is the shape parameter, and λ and γ are scale parameters.

[a] Covariates were added on the hazard function:
$h(t) = h_0(t) \times e^{\theta_1 \times (SOFA-6) + \theta_2 \times (Age-65) + \theta_3 \times No\_Acinetobacter\_Pseudomonas + \theta_4 \times (c_{avg.\ 120h}/MIC_{colistin}-5)}$, where θ_i is the covariate coefficient.

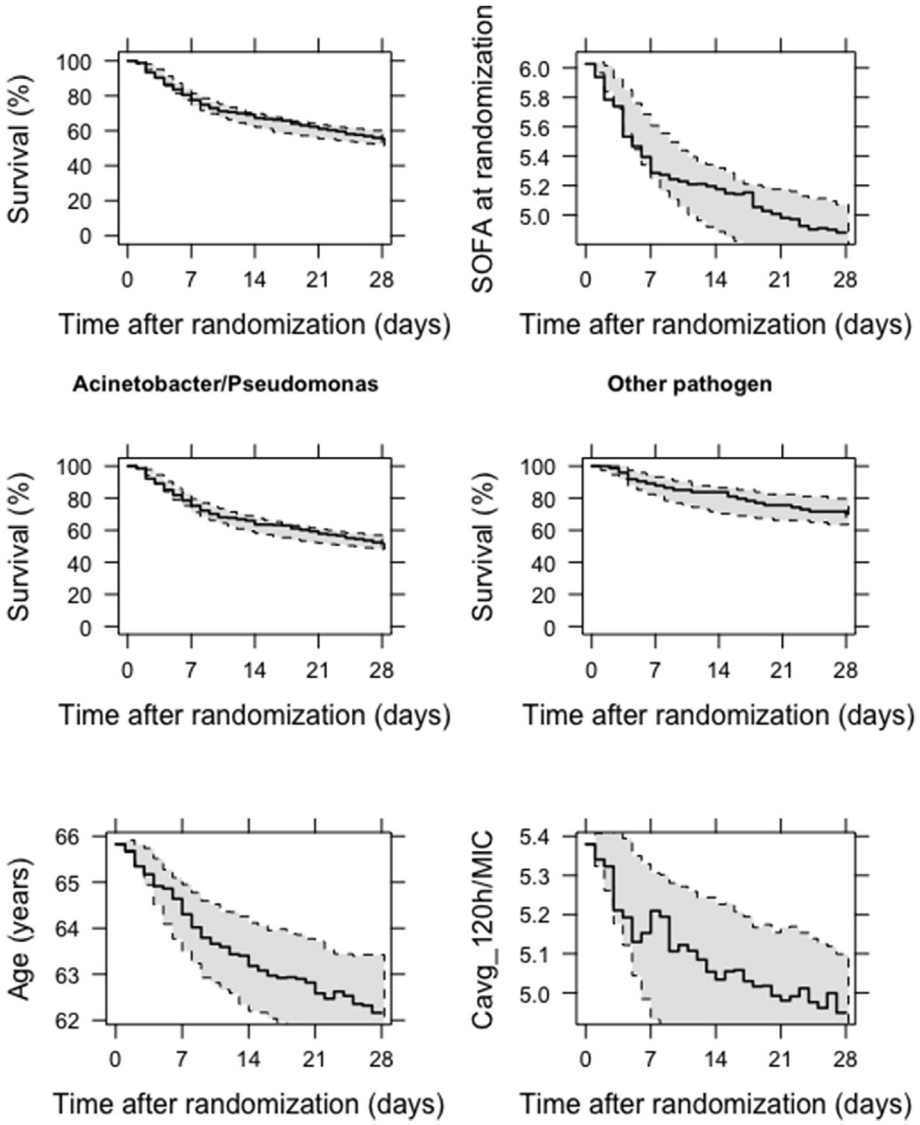

Fig. 4. Model evaluation of the final time-to-event model of survival. Kaplan–Meier Visual Predictive Check of the overall model (top left), and stratified for bacteria type (middle left and middle right) and Kaplan–Meier mean covariate plot [24] for SOFA score (top right), age (lower left) and ratio between average colistin concentration and MIC (lower right) where the means of the covariates on the y-axes are computed for those patients remaining in the trial at the times of events. The black lines illustrate the observed data, and the shaded intervals represent the 95% confidence intervals based on simulations from the developed model.

concentrations ≥2 mg/L, but without a loading dose the corresponding number would have been 7%, and it would have taken 25 hr before 66 % of the patients reached the same concentration target. Nevertheless, for indications such as bloodstream infection, the delay in formation of active drug, even after administration of a loading dose, might be a shortcoming for treatment with colistin. The dose

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reduction formula for patients with CrCL <50 mL/min [8] resulted in similar concentrations as for patients with CrCL of 50–80 mL/min (Fig. 2), while a more recent dose adjustment formula [9] would have resulted in higher concentrations.

The current study shows that the high failure rate and mortality observed in the AIDA trial [4] is likely not to be due to underdosing or failure to achieve the suggested PKPD target of 2 mg/L [9]. Moreover, of patients with both PK and colistin MIC determined, 74% (250/336) had an $AUC_{24h}/MIC \geq 48$. It should be noted that these targets are based on studies in mouse thigh infection models [15], while 55% of the patients in AIDA had pneumonia. Indeed, stasis was not achievable in the mouse lung model for two out of three strains (MICs of 0.5–1 mg/L) of *A. baumannii* [15], the most common bacterial species in the trial. We also identified *A. baumannii* (and *P. aeruginosa*) to be related to higher hazard of death than infections with e.g. *Klebsiella pneumoniae* (Table 1). Moreover, the freely available concentration of colistin in lung might be low because of poor distribution [16,17] or binding to mucin in lung fluids [18]. When the relationship between colistin concentration (or colistin concentration to MIC ratio) and the hazard of death was explored to be U-shaped to allow for reduced hazard at target concentrations of 2–4 mg/L, there was no significant improvement in the model fit.

As anticipated, patient characteristics, best described by SOFA score, was the most significant variable predicting time to death. That a low colistin exposure (i.e. low $C_{avg,120h}/MIC_{colistin}$ ratio) was associated with survival, even after correction for SOFA score, age and pathogen, is in line with an earlier study in 59 patients [19] where SOFA score and colistin concentrations were higher in patients who failed therapy. Their measured colistin trough concentrations (though reported as $C_{ss,avg}$ [19]) were however lower than the 10-hr post-dose concentrations observed here. This is likely to be primarily because of lower daily CMS dosing (median 3 MU) and extended dosing intervals (up to 36 hr). Their patients also had a median SOFA score of 2 vs 6 in the current study. These studies taken together indicate that individualized colistin dosage, guided by colistin exposure in blood, may not necessarily improve the outcome. It should also be acknowledged that residual confounding cannot be ruled out in both studies. To fully elucidate the exposure–response relationship, a study randomized by dose or concentration would be required, which is not feasible in practice.

Population PK analyses of colistin have earlier been reported in critically ill patients [5–8,20]. Different parameterizations (e.g. CrCL relationships) make comparisons of apparent colistin CL estimates difficult, but analyses of studies conducted a decade ago generally predict lower concentrations than analyses based on more recently conducted trials. This may at least partly be because of the lower fraction of measurable colistin components in earlier formulations [21] than in current products [7] (2nd International Conference on Polymyxins, Abstract P-2). For a patient with a CrCL of 80 mL/min, the current study predicts an average steady-state colistin concentration of 4.4 mg/L, for in total 9 MU per day, which is somewhat higher than relatively recent studies of 3.4 [20] and 2.7 [7] mg/L, but lower than Magréault et al. (4.3 mg/L; 28th European Congress of Clinical Microbiology and Infectious Diseases, Abstract P2232) considering their average CrCL of 99 mL/min. Inter-study difference might also be associated with patient status, although here CrCL was a better covariate than SOFA score for colistin clearance. A relationship between colistin clearance and CrCL has indeed earlier been suggested [8] despite the fact that polymyxins are eliminated by renal excretion only to a minor extent [9]. CrCL reflects however the overall kidney function, and, as for other peptides, the kidney may be an essential site for degradation of colistin [22].

$C_{avg,120h}/MIC_{colistin}$ was a superior predictor of fatality than all renal function variables tested, indicating that colistin exposure may better reflect prognosis. When CrCL was the only predictor in the model, and this relationship was fixed, the addition of $C_{avg,120h}/MIC_{colistin}$ did not reach statistical significance, indicating overlapping explanatory value. Future analyses of AIDA trial data may guide how to reduce the risk for colistin-induced acute kidney injury [23]. If individual dose adjustments based on concentration measurements are to be performed, the here identified sampling time points of 45 minutes and 10 hr are recommended when both colistin and CMS can be reliably assayed.

To conclude, the observed colistin concentrations were >2 mg/L in the majority of patients with CrCL <120 mL/min, while for patients with CrCL ≥120 mL/min higher doses would be needed to achieve the same exposure. The population PK model identified that both CMS and colistin clearances are highly correlated to CrCL, and explained parts of the variability in the exposure between patients. Patient health status, rather than colistin exposure, seems however most critical for treatment success in vulnerable patient populations such as the one studied in the colistin AIDA trial.

Transparency Declaration

Conflict of interest: Dr Brill is currently an employee at QPS Netherlands B.V. Dr Andini reports personal fees from Nordic Pharma, outside the submitted work. Dr Durante-Mangoni reports grants and personal fees from Pfizer, grants and personal fees from MSD, personal fees and non-financial support from Angelini, personal fees from Nordic Pharma, personal fees from Sanofi-Aventis, personal fees from Roche, outside the submitted work. Dr Bitterman reports grants from Rambam Health Care Campus. Dr Daikos reports grants from EU FP7, during the conduct of the study; grants and personal fees from Pfizer, personal fees from Menarini, personal fees from MSD, outside the submitted work; Dr Carmeli reports grants from FP7 European Commission, during the conduct of the study; grants and personal fees from MSD, grants and personal fees from Pfizer, grants and personal fees from Allecra Therapeutics, personal fees from Nabriva, personal fees from Roche, grants from Shinogi, outside the submitted work. Dr Friberg reports grants from EU FP7, grants from Vetenskapsrådet/JPIAMR, grants from Uppsala Antibiotic Centre (at Uppsala University), during the conduct of the study; grants from IMI ENABLE, outside the submitted work. All other authors report nothing to disclose. This work was supported by the FP7 EU-project AIDA (grant number Health-F3-2011-278348). M.B. and V.R. were also partly supported by JPIAMR and Vetenskapsrådet (the Swedish Research Council) (grant numbers 2015-06826 and 2018-03296) and Uppsala Antibiotic Centre (competitive grant from Uppsala University) to L.F. The work at Rambam and Beilinson was supported also by the Israel Ministry of Science and Technology (grant number 312075).

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Author contributions

All authors (1) contributed to the design of the study, acquisition, or analysis of data, (2) drafted or revised the article for intellectual content, and (3) approved the final version.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2020.03.016.

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