

Population pharmacokinetics of colistimethate sodium following intravenous administration in critically ill South African adults



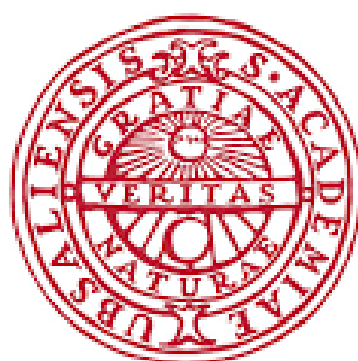
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Background

- The rise of multidrug resistant gram-negative bacterial (MDR-GNB) infections over recent years have led to the renewed use of colistin in clinical practice as “salvage” therapy. [1]
- In South Africa, colistin, a polymyxin E antibiotic, is an affordable option to treat MDR-GNB infections. [2-4]
- Colistin is administered as a prodrug, colistimethate sodium (CMS) (**Figure 1**). [5]
- Critically ill patients are the primary recipients of colistin and may have altered CMS exposures due to pathophysiological changes.
- Data on colistin pharmacokinetics in African populations are lacking.
- The objectives of this study were i) to characterize the pharmacokinetics of CMS in critically ill South African adults using a population approach, and ii) to explore covariates that influence CMS pharmacokinetics.

Methods

- 9 million units (MU) or 12 MU CMS loading dose administered followed by 12 hourly maintenance doses
- 24 critically ill, adult patients
- Blood samples collected at 1, 2, 4, 8, 12, 24 and 48 hours post loading dose
- CMS concentrations analysed using LCMS at Stellenbosch University
- Non-linear mixed effects modeling using NONMEM (version, 7.5.1, ICON development solutions)



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Covariates of interest: Weight, creatinine clearance (CRCL) estimated glomerular filtration rate (eGFR), albumin, inflammatory markers (c-reactive protein and white cell count), admission-type (e.g. medical, surgical, or burns patients) and sex.

Results

- A total of 154 samples from 24 critically ill patients were used in the modeling process. The cohort is described in **Table 1**.
- 31% of CMS concentrations were below limit of quantification (BLQ).
- The M3 method was used to handle BLQ data.
- A two-compartment model with first order elimination best described the CMS concentrations (**Table 2 and Figure 2**).
- eGFR was identified as a significant covariate.
- Admission type was not identified as a significant covariate on any parameter.

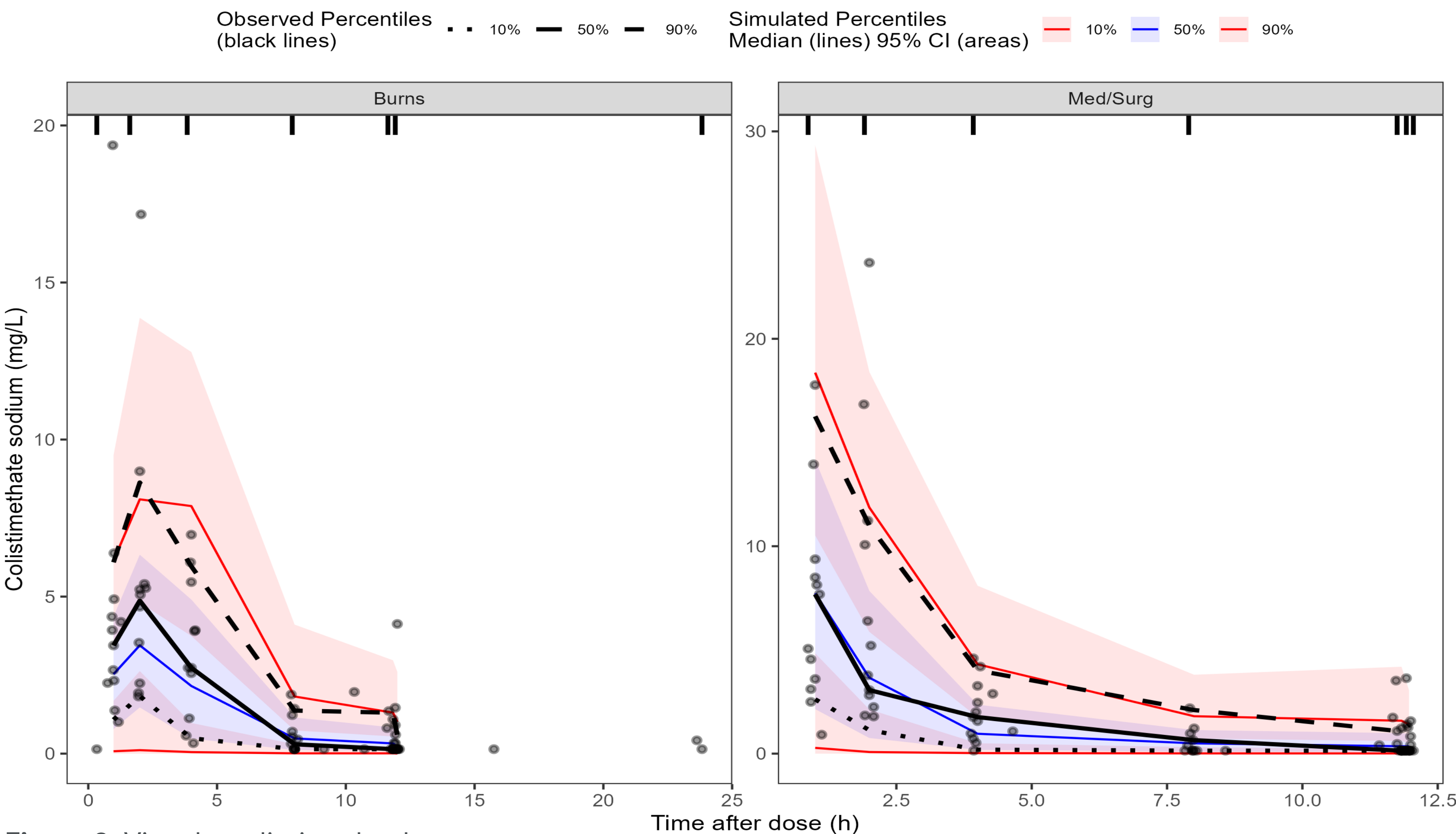


Figure 2. Visual predictive check

Conclusion

EGFR was found to be a significant covariate. Future analyses will integrate colistin data (active metabolite) to further explore the exposure of the active metabolite colistin and the influence of eGFR. Simulation scenarios with both augmented and impaired renal function will be conducted for dose optimization of CMS in critically ill patients.

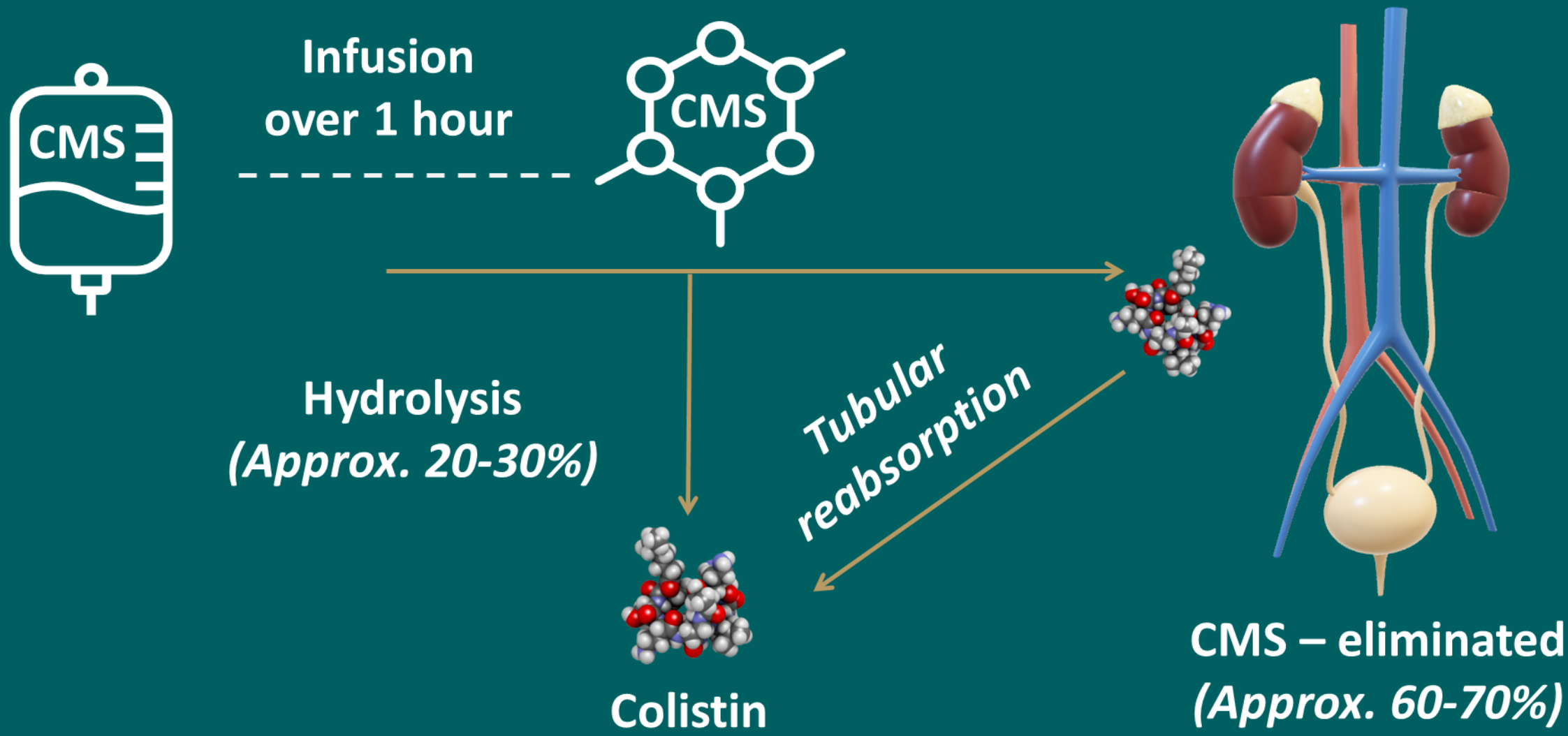


Table 1. Baseline characteristics

Characteristic	N=24
Male, n(%)	17 (71)
Weight (kg)	82.4 ± 14.34
Age (years)	42.4 ± 16.3
Patients admitted with burns, n (%)	12 (50)
Evidence of shock, n (%)	6 (25)
White cell counts, (× 10 ⁹ /L)	14.5 ± 6.6
C-reactive protein, (mg/L)	201.6 ± 100
Serum creatinine, (μmol/L), median (IQR)	68.5 (44.5 – 73.5)
Albumin, (g/L)	24.5 ± 4.9
Creatinine clearance (mL/min)	140 ± 58.7
Glomerular filtration rate (mL/min/1.73m ²) [#]	101.3 ± 37.7
[#] CKD-Epi 2021 equation	

Table 2. Final model parameters

Parameter	Estimate (relative standard error [RSE], %)
Central volume of distribution, Vd, (L)	18.9 (13.3)
Central clearance, CL, (L/hr)	8.95 (15.5)
Intercompartmental clearance, Q, (L/hr)	5.79 (19.2)
Peripheral volume of distribution, Vd, (L)	61.2 (43)
Interindividual variability (IIV)	
IIV on CL of CMS	0.264 (31.6)
Covariates	
eGFR on CMS CL* (fractional change per mL/min/1.73m ²)	1.06 (29.4)
Residual variability	
Proportional error (SD)	0.775 (8.8)

All clearance and volume parameters were allometrically scaled based on body weight, normalized to 80kg with fixed exponents of 0.75 and 1 for clearance and volume terms, respectively. *Estimated glomerular filtration rate was included as a covariate on CL as an exponential form. The covariate effect represents the fractional change in CL CMS per unit fractional change in eGFR, centered at 101 mL/min/1.73m².

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