



# Is there a need to monitor colistin exposure in critically ill patients?

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## Introduction

Colistin which is widely used to treat carbapenem resistant organisms is known to cause nephrotoxicity<sup>1</sup>. Wide inter-individual variability is observed with colistin exposure in patients<sup>2</sup>. There is no consensus on the need for routine monitoring of colistin for improving survival among critically ill patients.

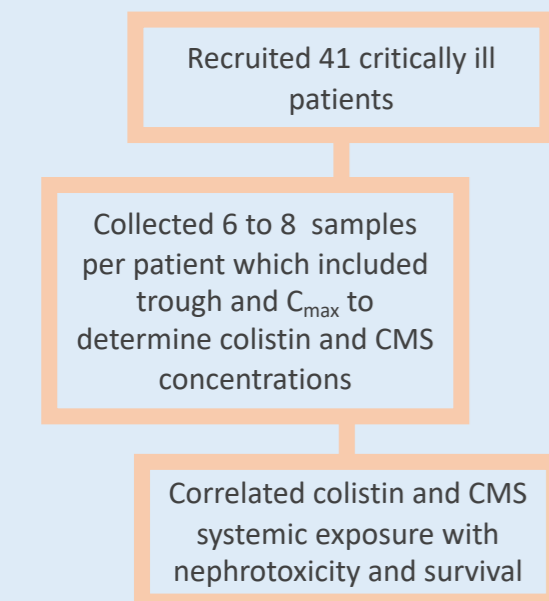
## Objectives

To correlate the systemic exposure of colistin with nephrotoxicity and overall survival in critically ill patients.

## Methodology

A prospective observational study was performed in 41 critically ill patients. Systemic exposure to colistin was determined (LC-MS/MS) after the first day of colistimethate sodium administration by collecting 6 to 8 blood specimens in the inter-dose interval

Acute Kidney Injury (AKI) was assessed by Kidney Disease: Improving Global Outcomes (KDIGO) score on the day of estimation of colistin exposure, day 3 and day 7 of colistin therapy.



## Results

Only 17.1% of patients had colistin AUC<sub>0-24h</sub> in the range of 50 – 60 mg.h/L. Colistin trough and CMS AUC<sub>0-24h</sub> correlated with GFR (R<sup>2</sup> = 0.28 and 0.26 respectively, p<0.001).

Incidence of Acute Kidney Injury (32.5%)

### Significant predictors of Acute Kidney Injury

Predictors	Odds ratio	95% Confidence interval	p value
Male sex <sup>3</sup>	2.16	1.19, 3.90	0.013*
Colistin trough	1.13	1.04, 1.22	0.004*
Serum albumin	0.58	0.37, 0.92	0.022*
Arterial pH	0.00	0.00, 0.03	0.001*
APACHE II	1.02	0.98, 1.06	0.439
SOFA score	1.14	1.04, 1.24	0.006*
Duration of colistin treatment (days)	1.08	0.98, 1.19	0.113

### ROC cutoffs to predict nephrotoxicity.

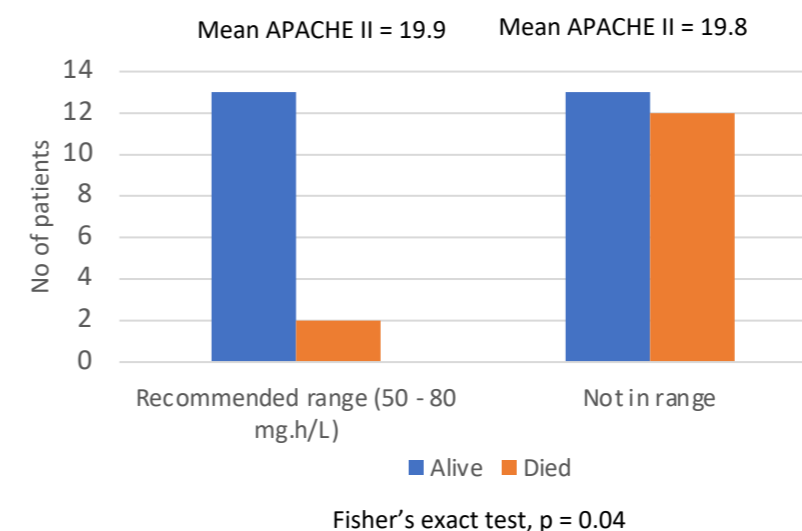
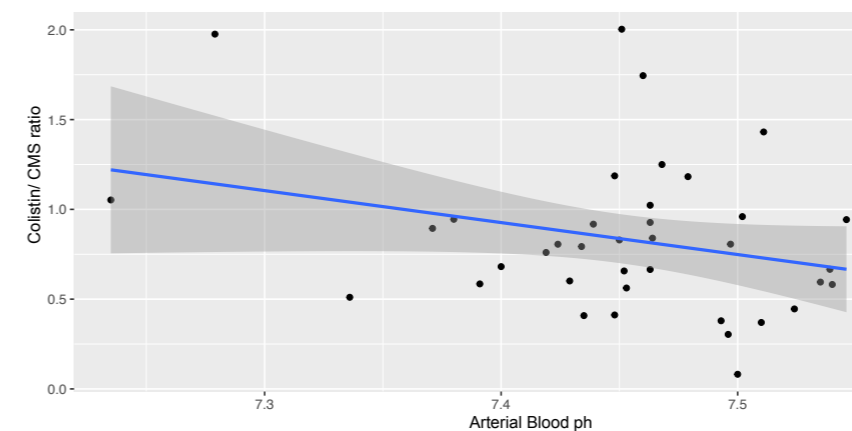
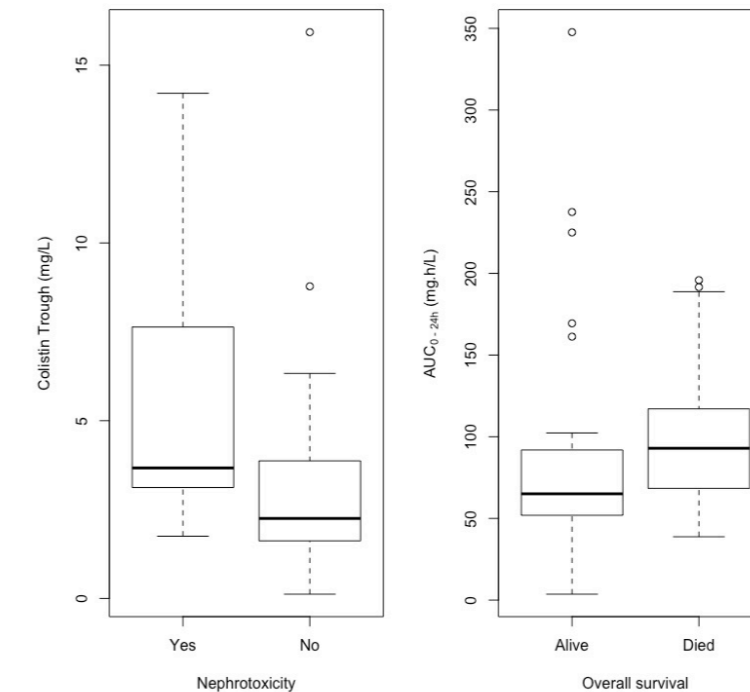
Predictors	Threshold	Specificity	Sensitivity	AUC
Colistin trough (mg/L)	3.0	0.67	0.83	0.75
Serum albumin (g/dL)	1.9	0.85	0.50	0.66
Arterial pH	7.43	0.85	0.50	0.63
SOFA score	7.5	0.76	0.75	0.81

65.9 % of patients (n = 27/41) survived till discharge from critical care unit, for the entire duration of treatment in the intensive care unit.

Colistin AUC<sub>0-24h</sub> was lower (closer to recommended therapeutic range) in patients who survived (median (IQR) = 65.1 mg.h/L (51.9 - 91.9)) in comparison to those who died (median (IQR) = 92.9 mg.h/L (71.8 – 114.1), p value = 0.08)

### Significant predictors of Overall survival

Predictors	Odds ratio	95% Confidence interval	p value
APACHE II	0.81	0.64, 0.96	0.036*
Mean SOFA score	0.73	0.47, 1.02	0.098
Serum albumin	55.19	3.94, 3398.58	0.016*
Colistin AUC <sub>0-24h</sub>	0.98	0.95, 1.00	0.087
Colistin:CMS AUC <sub>0-24h</sub> ratio	102.70	1.95, 60957.14	0.061
Arterial pH	>10 <sup>8</sup>	24.7, 10 <sup>20</sup>	0.051



## Conclusion

First time to suggest clinical usefulness of Arterial pH to predict nephrotoxicity: Arterial pH associated with nephrotoxicity when treated with colistin: < 7.43 mg/L

Significant predictor of nephrotoxicity: Colistin trough: >3 mg/L

Significant difference in survival: Colistin AUC<sub>0-24h</sub>: Recommended range: 50 – 80 mg.h/L

Proportion of patients in therapeutic range of Colistin AUC<sub>0-24h</sub>: Only 37.5%

TDM should ideally be performed when colistin is prescribed

## References

- Gai Z, Samodelov SL, Kullak-Ublick GA, Visentin M. Molecular Mechanisms of Colistin-Induced Nephrotoxicity. *Molecules*. 2019;24(3):653. Published 2019 Feb 12. doi:10.3390/molecules24030653
- Nation RL, Garonzik SM, Thamilikitul V, et al. Dosing guidance for intravenous colistin in critically-ill patients. *Clin Infect Dis*. 2017;64(5):565-571. doi:10.1093/cid/ciw839
- Spapen H, Jacobs R, Van Gorp V, Troubleyn J, Honoré PM. Renal and neurological side effects of colistin in critically ill patients. *Ann Intensive Care*. 2011;1(1):14. Published 2011 May 25. doi:10.1186/2110-5820-1-14
- Moni M, Sudhir AS, T S D, et al. Clinical efficacy and pharmacokinetics of CMS 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 [published online ahead of print, 2020 Aug 8]. *Int J Infect Dis*. 2020;S1201-9712(20)30638-X. doi:10.1016/j.ijid.2020.08.010

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