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Coadministration of minocycline with colistin in critically ill patients is associated with reduced incidence of acute renal failure

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Background: The lack of available agents with demonstrated clinical efficacy against infections due to multidrug-resistant gram-negative bacteria (MDR-GNB) has resulted in an increased use of last-resort antibiotics such as colistin (COL), though its nephrotoxic effects are well-known. Minocycline (MIN) has activity against some MDR-GNB, and synergistic activity with polymyxins has been shown in vitro. Nonclinical studies have suggested oxidative damage, caspase-mediated apoptosis, and iNOS levels may be involved in the pathogenesis of COL-associated acute renal failure (ARF). Minocycline (MIN) inhibits caspase 1, caspase 3, and iNOS, leading to the hypothesis that coadministration of MIN with COL may reduce incidence of ARF in patients receiving the combination.

Material/methods: A retrospective cohort study of patients who received COL without MIN or in combination with MIN was conducted using the Premier Research database. Inclusion criteria: (1) age ≥18 years, (2) admitted to an intensive care unit (ICU) at time of COL initiation, (3) primary ICD-9 diagnosis of pneumonia or sepsis, and (4) discharged between Jan 2010-Dec 2015. ICD-9 code 584.XX or ICD-10 code N1 were used to define ARF. Baseline comparisons, 1:8 propensity score matching (PSM), and confirmatory logistic regression analyses were conducted. PSM was conducted using nearest neighbor matching with exact matches on baseline renal disease and region. Regression variables included age, gender, race, diagnosis, use of meropenem or tigecycline, discharge year, hospital size, region, payor type, 17 individual Charlson comorbidities, other medications associated with ARF, length of stay (LOS) prior to initiation of study drugs, and mechanical ventilation use.

Results: 5,120 patients received COL and met inclusion criteria; 95 of these patients received MIN in combination with COL (COL-MIN). In PSM analysis, 86 (90.53%) of COL-MIN coadministration patients were matched 1:8 with 688 patients receiving COL without MIN. Unadjusted, PSM, and logistic regression analyses all showed that patients that received COL-MIN were less likely to develop

ARF compared to COL without MIN (Table). Mortality and 30-day readmission rates were similar between groups in unadjusted and adjusted analyses. ARF rate was not impacted by prevalence of baseline renal disease.

	COL	**COL-MIN**	**OR (95% CI)**	**P-value**
Unadjusted Outcomes	n=5025	n=95		
ARF	23.0%	11.6%	0.438 (0.233, 0.825)	0.009
Mortality	29.9%	31.6%	1.085 (0.701, 1.679)	0.715
30-day readmission	23.0%	11.6%	0.438 (0.233, 0.825)	0.009
PSM (1:8 matching)	n=688	n=86		
ARF	24.7%	11.6%	0.401 (0.203, 0.793)	**0.007**
Mortality	32.0%	32.6%	1.027 (0.636, 1.657)	0.913
30-day readmission	28.0%	29.3%	1.067 (0.585, 1.944)	0.833
Logistic regression model	n=5,025	n=95		
ARF			0.390 (0.202, 0.753)	**0.005**
Mortality			0.913 (0.577, 1.447)	0.699
30-day readmission			1.112 (0.646, 1.915)	0.702

Conclusions: Coadministration of MIN with COL in ICU patients may reduce the occurrence of colistin-associated ARF. Further clinical evaluation of this combination in prospective studies is warranted.