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

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Abstract

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.

Materials/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, payer 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. 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.

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.

Introduction and Purpose

The prevalence of serious infections due to highly resistant gram-negative pathogens are increasing worldwide.[1,2,3]

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, though the occurrence of acute renal failure (ARF) with colistin use remains problematic.[4]

Minocycline is a member of the tetracycline class of antibiotics with broad-spectrum activity against many gram-positive and gram-negative bacteria. Its 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 ARF. Minocycline inhibits caspase 1, caspase 3, and iNOS, leading to the hypothesis that coadministration of minocycline with colistin may reduce incidence of ARF.

We used a large, representative hospital database to test the hypothesis that patients in the intensive care unit (ICU) who received colistin in combination with minocycline have lower occurrence of ARF relative to patients who received colistin without minocycline.

Methods

Study Design:

It was a multi-center retrospective cohort study using the Premier Research Database to examine the impact of minocycline coadministration with colistin on ARF.

Data Source:

Data was extracted from the Premier Research Database, one of the largest US hospital clinical and economic databases.

The Premier Research Database contains data from more than 500 acute care hospitals, representing all geographical areas, a broad range of bed sizes, and teaching, nonteaching, urban, and rural facilities. It also contains all patient-level, day-of-service billed items, including procedures, medications, laboratory, and diagnostic and therapeutic services delivered within the hospital.

Study Population:

Study population consisted of all adult patients who met all inclusion criteria listed below:

- Age ≥18 years;
- Hospitalized with a primary diagnosis of pneumonia or sepsis;
- Had at least one day of intensive care unit (ICU) stay during colistin administration;
- Received either colistin without minocycline (COL) or minocycline coadministration with colistin (COL-MIN).
- Received a minimum of three days of intravenous (IV) colistin with or without coadministration of minocycline;
- In COL-MIN cohort, the overlap of colistin and minocycline must have occurred for >=3 days;
- Discharged between Jan. 1, 2010 and Dec. 31, 2015;

Patients with a diagnosis of cystic fibrosis were excluded from the analysis.

Pneumonia was identified by the principal diagnosis ICD-9-CM codes 480-486 (ICD-10-CM codes J12-J18), or by respiratory failure ICD-9-CM codes 518.81 or 518.84 (ICD-10-CM codes J96.0X or J96.2X) with pneumonia as a secondary diagnosis. Sepsis was identified by the principal diagnosis codes 038, 038.9, 790.7, 995.91, 995.92 or 785.52 (ICD-10-CM codes A41, R78.81, R65.1X, or R65.2X), or by respiratory failure codes with sepsis as a secondary diagnosis. Cystic fibrosis was identified by the diagnosis ICD-9-CM codes 277.0X (ICD-10-CM codes E84).

Outcomes of Interest:

The primary outcome of interest was frequency of ARF, defined as ICD-9-CM codes of 584 (ICD-10-CM codes N17). Secondary outcomes included in-hospital mortality, 30-day all-cause hospital readmission, and costs and length of stay (LOS) attributed to ARF.

Statistical Analyses:

Baseline characteristics were summarized and compared between patients receiving COL versus COL-MIN.

Discrete data were reported as frequencies and percentages; continuous data were reported as mean, standard deviation (SD), median, and interquartile range.

Differences between treatment groups were tested using Mann-Whitney U test for continuous variables, and the Chi-square or Fisher's exact test (for cell counts <5) for categorical variables.

Propensity score matching (PSM) technique and confirmatory logistic regression model were implemented.

PSM was conducted where each COL-MIN patient was matched to 8 COL patients within a caliper width of 0.2 logit of SD under the condition of exact matches on baseline renal disease and region (west and south were combined).

Potential risk factors in regression model included age, gender, race, diagnosis, use of meropenem or tigecycline, discharge year, hospital size and 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.

Incremental costs and attributable LOS associated with ARF was explored using propensity score matching with a 1:1 matching ratio (patients with vs. without ARF, regardless of treatment group) and confirmatory conventional regression models.

All data and analyses were performed using SAS Version 9.2 (SAS Institute Inc., Cary, NC).

Results

A total of 95 COL-MIN and 5,025 COL patients met all inclusion and exclusion criteria and were included in the study.

- Compared to COL, COL-MIN patients were older (64.5 vs. 61.3), and more likely to have chronic renal disease (51.6% vs. 39.5%) and to receive other medications during hospitalization which could cause acute renal failure (92.6% vs. 84.2%). However, other baseline characteristics and comorbidities were quite similar between groups (**Table 1**).
- Hospital characteristics varied between groups, with COL-MIN patients more likely to be treated at South (90.5% vs. 54.9%) or urban hospitals (100% vs. 95.0%) and COL patients more likely to be treated at teaching hospitals (38.9% vs. 52.2%) (**Table 1**).
- Patients in the COL-MIN group received more days of colistin compared to those in the COL group (13.2 vs. 10.0 days).
- Mean (median) days of colistin and minocycline overlap in the COL-MIN group was 7.36 (6).
- In the COL-MIN group, minocycline was initiated prior to colistin therapy in 9 (18.9%) of cases, after colistin in 43 (45.3%) of cases, and concomitantly with colistin in 34 (35.8%) of cases.
- 919 (17.9%) patients had microbiological data available. The most commonly reported pathogens included Enterobacteriaceae (n=522, 56.8%), *Pseudomonas aeruginosa* (n=425, 46.3%), and *Acinetobacter baumannii* (n=400, 43.5%).
- Without risk factor adjustment, COL-MIN patients were significantly less likely to experience ARF compared to COL patients (11.6% vs. 23.0%). In-hospital mortality and 30-day all-cause re-admission were similar between groups (**Table 2**). ARF rates were consistently and numerically lower in COL-MIN patients regardless the length of colistin duration; similar findings were observed in those patients with (10.2% vs. 20.6%) and without (13.0% vs. 24.6%) baseline chronic renal disease (**Table 3**).
- PSM results were consistent with the unadjusted analysis: patients receiving COL-MIN were less likely to experience ARF compared to those receiving COL (11.6% vs. 24.7%, OR 0.401, p=0.007). Confirmatory logistic regression found an odds ratio of 0.390 for ARF in COL-MIN vs. COL patients (p=0.005). Both PSM method and conventional logistic regression modeling technique confirmed that mortality and 30-day readmission rates remained similar between groups (**Table 2**).
- 1,062 patients with ARF were matched 1:1 to patients without ARF. Attributable costs and LOS associated with ARF were $11,668 (p<0.001) and 1.44 days (p=0.097, NS), respectively. Similar results were confirmed with conventional logistic regression: ARF was associated with an incremental cost increase of $10,308 and an additional 3.40 days LOS (p<0.001 for both; **Table 4**).

Table 1: Demographic and baseline characteristics

	Primary Population			PSM Population		
Variable	COL (N=5,025)	COL-MIN (N=95)	P-value	COL (N=688)	COL-MIN (N=86)	Absolute Standardized Difference
Age (years)						
Mean±SD	61.3 ± 15.9	64.5 ± 16.1	**0.046**	64.1 ± 14.2	64.0 ± 16.1	0.3%
Median (Q1, Q3)	63 (52, 73)	65 (57, 76)		65 (56, 74)	65 (56, 74)	
Male, %	58.2%	49.5%	0.090	49.3%	50.0%	1.5%
White, %	58.1%	62.1%	0.555	61.5%	64.0%	5.1%
Primary payers, %						
Medicare	62.1%	64.2%	0.465	62.6%	64.0%	2.7%
Medicaid	19.0%	15.8%		18.6%	17.4%	3.0%
Commercial/Managed	13.9%	16.8%		12.8%	15.1%	6.7%
CCI score						
Mean±SD	3.2 ± 2.3	3.3 ± 2.3	0.545	3.2±2.0	3.2±2.2	2.0%
Median (Q1, Q3)	3 (2, 5)	3 (2, 4)		3 (2, 4)	3 (2, 4)	
Common comorbidities, %						
Myocardial infarction	9.1%	6.3%	0.356	6.5%	5.8%	3.0%
Congestive heart failure	32.4%	36.8%	0.360	36.5%	37.2%	1.5%
Peripheral vascular disease	12.0%	9.5%	0.455	9.7%	10.5%	2.4%
Cerebrovascular disease	11.0%	7.4%	0.263	8.3%	8.1%	0.5%
COPD	37.8%	34.7%	0.543	35.0%	36.0%	2.1%
Diabetes w/o complication	36.7%	32.6%	0.411	38.4%	34.9%	7.2 %
Diabetes w/ complication	7.7%	3.2%	0.117	3.1%	3.5%	2.5%
Paraplegia & hemiplegia	14.6%	14.7%	0.980	16.4%	16.3%	0.4%
Chronic renal disease	39.5%	51.6%	**0.018**	47.7%	47.7%	0.0%
Region, %						
Midwest	19.3%	8.4%	**0.002**	9.3%	9.3%	0.0%
Northeast	16.0%	0.0%		0.0%	0.0%	0.0%
South	54.9%	90.5%		88.4%	89.5%	3.7%
West	9.7%	1.1%		2.3%	1.2%	8.9%
Urban, %	95.0%	100.0%	**0.015**	100.0%	100.0%	0.0%
Teaching, %	52.2%	38.9%	**0.011**	45.6%	41.9%	7.6%
Bed size, %						
0 – 299	26.5%	34.7%	**0.006**	30.0%	30.2%	0.3%
300 – 499	40.5%	33.7%		34.2%	36.0%	6.0%
500+	33.1%	31.6%		35.8%	33.7%	4.3%
Infection type, %						
Pneumonia	73.9%	68.4%	0.226	71.9%	70.9%	2.3%
Sepsis	85.9%	88.4%	0.485	87.6%	89.5%	5.9%
Other medications which could cause ARF, %	84.2%	92.6%	0.026	91.4%	91.9%	1.6%

PSM; propensity score matching. COL; colistin. COL-MIN; colistin-minocycline. SD; standard deviation. CCI; Charlson comorbidity index. COPD; chronic obstructive pulmonary disease.

Table 2: Unadjusted and adjusted outcomes in patients treated with COL or COL-MIN

	COL	COL-MIN	OR (95% CI)	P-value	C-statistic
Unadjusted Outcomes	n=5025	n=95			
ARF, %	23.0%	11.6%	0.438 (0.233, 0.825)	**0.009**	
In-hospital mortality, %	29.9%	31.6%	1.085 (0.701, 1.679)	0.715	
30-day readmission, %	27.0%	30.8%	1.205 (0.708, 2.051)	0.492	
PSM (1:8 matching)	n=688	n=86			
ARF, %	24.7%	11.6%	0.401 (0.203, 0.793)	**0.007**	
In-hospital 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**	0.681
In-hospital mortality			0.913 (0.577, 1.447)	0.699	0.711
30-day readmission			1.112 (0.646, 1.915)	0.702	0.598

PSM; propensity score matching. OR; odds ratio. CI; confidence interval. ARF; acute renal failure.

Table 3: Effect of number of days on COL/COL-MIN and chronic renal disease status on unadjusted incidence of acute renal failure

		Unadjusted ARF Rate		
Risk Factor	Category	COL	COL-MIN	P-value
Duration of colistin treatment	3-5 days	305/1596 (19.1%)	2/21 (9.5%)	0.401
	6-8 days	268/1223 (21.9%)	2/19 (10.5%)	0.398
	9-13 days	283/1145 (24.7%)	3/27 (11.1%)	0.117
	≥14 days	300/1061 (28.3%)	4/28 (14.3%)	0.135
Chronic renal disease status	Yes	410/1987 (20.6%)	5/49 (10.2%)	0.073
	No	746/3038 (24.6%)	6/46 (13.0%)	0.071

Table 4: Attributable cost and length of stay associated with acute renal failure

	Patients without ARF	Patients with ARF	Difference (95% CI)	P-value	C-stat
PSM	n=1,062	n=1,062			
Incremental costs* of ARF ($)	$61,535	$73,203	$11,668 (5,998, 17,338)	<0.001	
Incremental LOS* of ARF (days)	20.38	21.83	1.44 (-0.26, 3.15)	0.097	
Logistic regression model	n=3,953	n=1,167			
Incremental costs* of ARF ($)			$10,308 (7,691, 12,924)	<0.001	0.635
Incremental LOS* of ARF (days)			3.40 (2.16, 4.64)	<0.001	0.125

ARF; acute renal failure. PSM; propensity score matching. CI; confidence interval. LOS; length of stay.
*costs and LOS were calculated starting from the study drug initiation to discharge.

Limitations

- The available data were derived from administrative records rather than a prospectively defined and standardized data collection
- Inherent in most secondary database analyses, we assumed that hospitals reported patient information and treatment accurately and consistently and there was no source verification across with original medical charts.
- Full clinical details, such as clinical cure and chemistry lab results to define acute renal failure, are not available in the Premier database.
- Microbiology data were only available in a small subset of patients, so it is unclear if observed differences in ARF rates between treatment groups are biased due to differences in the invading pathogens.

Despite those limitations, the data were derived from a broad sample of both hospitals and patients which are representative of current real world use of colistin and coadministration with minocycline.

Conclusions

- Although studies clearly demonstrate that use of colistin results in increased incidence of ARF, particularly in critically ill patients, clinicians have few available options for treating patients with these life-threatening infections due to MDR-GNB.
- The findings from this large, representative, retrospective, multicenter cohort analysis suggest that coadministration of minocycline with colistin in critically ill patients may reduce the occurrence of colistin-associated ARF.
- This analysis also suggests that patients who experienced ARF had an approximate 3 day increase in hospital LOS and >$10,000 in excess hospital costs as substantial burden to patients and the healthcare system.
- Further clinical evaluation of this combination therapy strategy in prospective studies is warranted.

Disclosures

This study was funded by The Medicines Company.

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Presented at ECCMID 2017 (27th European Congress of Clinical Microbiology and Infectious Diseases) 22-25 April 2017, Vienna, Austria