Supplementary e-Appendix.

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Data analysis methods supplement

Effect modification modeling methods

Recognizing the importance of addressing potential confounding of the interaction analyses in our paper, we chose to use covariate adjustment to reduce any potential confounding of each interaction point estimate. This involved creating separate multivariable models for each interaction, with each model applying a change-in-estimate algorithm[1] to adjust the interaction point estimate. The rationale for this approach is that although propensity score matching ensures balance of covariates in colistin exposed vs. unexposed patients, it may not guarantee balance within strata of a given interaction; stratum specific PS models are not feasible for continuous variable interactions, and we wanted to use the same estimation approach for all interactions of interest. In addition, there is strong precedent for combining propensity score matching with covariate adjustment in the matched population, which falls under the umbrella of doubly robust estimation.[2] The variables hemoglobin, chloride, age, and glomerular filtration rate were modeled as continuous covariates in the interaction analyses. The rationale for this approach is that categorization of continuous variables during analysis leads to a loss of information.[3] For display of the results, we solved the regression equations for various values of each factor that have clinical relevance.

Effect modification covariate adjustment model specifications

1. Hemoglobin concentration
   - Adjusted for age, platelet count, race, admission type, anion gap, diabetes mellitus, baseline acute kidney injury status

2. Age
   - Adjusted for platelet count, sodium concentration, diabetes mellitus, heart failure, hypertension, anion gap, vancomycin exposure, angiotensin converting enzyme inhibitor / angiotensin receptor blocker exposure, immunosuppression exposure

3. Chloride concentration
   - Adjusted for age, platelet count, glomerular filtration rate, sodium concentration, anion gap, race, admission type, liver disease, hematologic malignancy

4. Glomerular Filtration Rate
   - Adjusted for platelet count, sodium concentration, diabetes mellitus, center, cardiac arrhythmia, immunosuppression exposure

5. Vasopressor exposure
   - Adjusted for platelet count, sodium concentration, center, diabetes mellitus, heart failure, anion gap

6. Statin exposure
   - Adjusted for diabetes mellitus, center, baseline acute kidney injury status, heart failure, hematologic malignancy

7. Vancomycin exposure
   - Adjusted for platelet count, sodium concentration, anion gap, race, intensive care unit admission, rheumatic disease

8. Aminoglycoside exposure
   - Adjusted for heart failure, diabetes mellitus, anion gap

Risk factor analysis in colistin exposed patients

We examined potential risk factors for acute kidney injury in patients exposed to colistin in the unmatched colistin group (n = 168). The unmatched (as opposed to the matched group) was used to maximize sample size and because the goal was not a comparison with controls in this analysis. Potential risk factors were first examined in univariate Poisson regression models. Candidate risk factor variables were age, race, total body weight, body mass index, intensive care unit admission, mechanical ventilation, baseline acute kidney injury, comorbidities (heart failure, hypertension, liver disease, diabetes mellitus, chronic kidney disease, myocardial infarction, peripheral vascular disease, malignancy, cystic fibrosis), vasopressor exposure, statin exposure, concomitant nephrotoxins (only drug exposures that overlapped with colistin exposure), baseline glomerular filtration rate, laboratory values (hemoglobin, sodium, chloride, bicarbonate, glucose), infecting organism, time to treatment, blood product administration, and colistin dose (mg/kg/day colistin base activity.

We then constructed a multivariable Poisson regression model for the association of each variable and acute kidney injury rate. Multivariable modeling proceeded with the variables that had a univariate association of $p < 0.25$.[4] The model was fit using a backwards selection procedure. Variables were eliminated individually by comparing the log likelihood ratio test for each model step and using the 5% significance level.[4] Variables eliminated were re-entered in the eventual final multivariable model to ensure that no omitted variable significantly reduced the log likelihood of the model, with a p-value of 0.1 for inclusion. The linearity of associations between continuous variables in the in final model and acute kidney injury rate were examined with fractional polynomial analysis,[4] with no deviations from linearity detected. Multicollinearity among the variables in the final model was checked with the variance inflation factor (VIF), which showed an average VIF of 1.07 and with no variable showing a value greater than 1.15. Lastly, the final model was checked for overdispersion with the Poisson goodness of fit test, with no evidence of overdispersion (p=0.50)

Table S1. KDIGO criteria

AKI level	Creatinine criteria
Stage 1	≥ 0.3 mg/dl increase within 48 hours –**or**— 1.5 - 1.9 x baseline within 7 days
Stage 2	2-2.9 x baseline
Stage 3	3 x baseline –**or**—increase in Scr to ≥ 4.0 mg/dl –**or**— renal replacement therapy

Methods for defining pre-exposure AKI episodes

Pre-exposure AKI was defined by applying the KDIGO criteria from hospital admission up to the time of exposure. Baseline creatinine was defined as the lowest value obtained within the first 48 hours of hospitalization. Because the impact of a prior AKI episode on future AKI risk during antibiotic treatment might depend on the timing of, and resolution of the prior episode, we further determined whether a prior AKI episode was resolved at the time of antibiotic exposure. We defined resolution as a return of creatinine concentration to within 25% of the baseline value. As stated in the primary text, patients that required renal replacement therapy within 14 days prior to the index date were excluded. The final pre-exposure AKI variable was thus coded as follows: No prior AKI, prior AKI that resolved, prior AKI that was unresolved (i.e. active AKI at the time of antibiotic exposure). As detailed in the primary text, we conducted supplementary analyses that were restricted to patients without any prior AKI episodes.

Table S2. Additional Baseline Covariates

Variable	Unmatched Cohort			Matched Cohort		
	Colistin n=168	Control n=1222	Standardized Difference[e]	Colistin n=150	Control n=150	Standardized Difference[e]
Comorbidities, n (%)						
Myocardial infarction	27 (16)	219 (18)	-0.05	26 (17)	26 (17)	0
Cardiac arrhythmias	96 (57)	680 (56)	0.03	88 (59)	89 (59)	-0.01
Valvular disease	24 (14)	217 (18)	-0.1	23 (15)	22 (15)	0.02
Peripheral vascular disease	30 (18)	241 (20)	-0.05	27 (18)	29 (19)	-0.03
Cerebrovascular disease	36 (21)	280 (23)	-0.03	30 (20)	28 (19)	0.03
Pulmonary circulation disorder	38 (23)	282 (23)	-0.01	34 (23)	30 (20)	0.06
Rheumatic disease	10 (6)	53 (4)	0.07	7 (5)	7 (5)	0
Peptic ulcer disease	12 (7)	77 (6)	0.03	11 (7)	11 (7)	0
Hemiplegia / paraplegia	25 (15)	169 (14)	0.03	24 (16)	24 (16)	0
Solid tumor malignancy						
Non-metastatic	12 (7)	141 (12)	-0.15	11 (7)	13 (9)	-0.05
Metastatic	10 (6)	117 (10)	-0.14	10 (7)	9 (6)	0.03
Hematologic malignancy	12 (7)	111 (9)	-0.07	12 (8)	8 (5)	0.11
AIDS/HIV	4 (2)	24 (2)	0.03	3 (2)	3 (2)	0
Dementia	7 (4)	57 (5)	-0.02	7 (5)	5 (3)	0.06
Cystic Fibrosis	16 (9)	84 (7)	0.1	14 (9)	17 (11)	-0.07
Transplant[a]	8 (5)	61 (5)	-0.01	8 (5)	6 (4)	0.06
Medications, n (%)						
Anti-VRE[b]	28 (17)	47 (4)	0.43	20 (13)	26 (17)	-0.11
Amphotericin	1 (0.6)	2 (0.2)	0.07	0 (0)	0 (0)	na
Other antifungals[c]	46 (27)	159 (13)	0.36	39 (26)	42 (28)	-0.05
Aspirin	39 (23)	336 (28)	-0.1	34 (23)	31 (21)	0.05
Statins	40 (24)	284 (23)	0.01	36 (24)	35 (23)	0.02
Corticosteroids	43 (26)	238 (19)	0.14	38 (25)	34 (23)	0.06
Other immunosuppression[d]	13 (8)	80 (7)	0.05	12 (8)	11 (7)	0.03

Parenteral Nutrition	37 (22)	159 (13)	0.24	31 (21)	29 (19)	0.03
Intravenous antiarrhythmics[e]	7 (4)	31 (3)	0.09	5 (3)	4 (3)	0.04
Laboratory						
Sodium, mEq/L, mean (SD)	139 (6.5)	138 (5.0)	0.19	139 (5.4)	139 (4.8)	0.05
Chloride, mEq/L, mean (SD)	106 (7.6)	104 (6.9)	0.14	105 (7.4)	105 (7.2)	0.05
Potassium, mEq/L, mean (SD)	4.1 (0.5)	4.1 (0.6)	0.11	4.1 (0.5)	4.1 (0.6)	0.03
Bicarbonate, mEq/L, mean (SD)	25.9 (6.0)	26.3 (5.2)	-0.07	26.3 (5.8)	26.5 (5.7)	-0.04
Anion gap, mEq/L, mean (SD)	12.1 (4.1)	11.8 (3.2)	0.09	11.9 (3.6)	11.8 (3.7)	0.04
Glucose, mg/dL, mean (SD)	139 (50.4)	140 (59)	-0.03	139 (52)	135 (44)	0.07
Prior hospital visits, n (%)						
None	50 (30)	358 (29.3)	0.01	43 (29)	44 (29)	-0.01
One to three	57 (34)	463 (38)	-0.08	51 (34)	48 (32)	0.04
More than three	61 (36)	401 (33)	0.07	56 (37)	58 (39)	-0.03

Notes: a- Transplant types include liver, lung, and heart; b- linezolid or daptomycin; c- fluconazole, voriconazole, or caspofungin; d- mycophenolate, methotrexate, any type of chemotherapy, azathioprine, or sirolimus; e- Standardized differences are a measure of covariate balance that are not effected by sample size. Values larger than 0.10 are considered evidence of meaningful imbalance. **Abbreviations-** med-median; IQR- interquartile range; AIDS- acquired immunodeficiency syndrome; HIV- human immunodeficiency virus; VRE- vancomycin resistant enterococcus; Difference between groups refers to the standardized difference.

Table S3. Control Antibiotics in the primary analysis

	Unmatched Cohort	**Matched Cohort**
Antibiotic	Frequency (%)	Frequency (%)
Cefepime	491 (40)	50 (33)
Levofloxacin	308 (25)	43 (29)
Meropenem	220 (18)	25 (17)
Piperacillin/tazobactam	95 (8)	6 (4)
Aztreonam	54 (5)	8 (5)
Ceftazidime	29 (2)	6 (4)
Ampicillin/sulbactam	25 (2)	12 (8)

Table S4. AKI incidence across control antibiotics

Antibiotic	**AKI incidence, n (%)**
Cefepime	13/50 (26)
Levofloxacin	7/43 (16)
Meropenem	7/25 (28)
Piperacillin/tazobactam	1/6 (17)

Aztreonam	1/8 (13)
Ceftazidime	1/6 (17)
Ampicillin/sulbactam	3/12 (25)

p = 0.901 for the difference across groups (Fisher's exact test)

Table S5. Colistin Dosing

	Dosing Frequency		
	Every 8 hours n=46, med (IQR)	Every 12 hours n=88, med (IQR)	Every 24 hours n=16, med (IQR)
GFR, mL/min/1.73 m^2	101 (78, 124)	86 (62, 118)	29 (27, 47)
Colistin dose			
million IU/day[a]	10.9 (9.0, 13.3)	9.9 (6.7, 11.7)	4.7 (3.7, 6.7)
mg/day	326 (270, 400)	295 (200, 350)	141 (110, 200)
mg/kg/day[b]	4.9 (4.3, 5.4)	4.5 (3.5, 5.4)	2.4 (1.9, 3.1)

a- 1,000,000 IU is equivalent to approximately 30 mg colistin base activity; b-Normalized to ideal body weight; med- median; IQR- interquartile range; IU-international units

Table S6. Analysis of KDIGO Stage 2 or higher: Rates and Rate Ratios

Outcome	**Colistin** n (rate/100 days)	**Control** n (rate/100 days)	**IRR** (95% CI)
Acute kidney injury			
End of follow up	47 (4.0)	15 (1.1)	3.7 (2.1-6.7)
72 hours	19 (4.5)	6 (1.4)	3.2 (1.3-8.0)

Analysis included 150 matched pairs. IRR- incidence rate ratio; CI- confidence interval

Table S7. Analysis of KDIGO Stage 2 or higher: Cumulative incidence and Risk Differences

Outcome	**Colistin** n (%)	**Control** n (%)	**Risk Difference*** (95% CI)
Acute kidney injury			
End of follow up	47 (31)	15 (10)	21 (13-30)
72 hours	19 (13)	6 (4)	9 (2-15)

Analysis included 150 matched pairs. *risk difference expressed as percentage; CI- confidence interval

Table S8. Analysis in Subgroup of Patients Free of Prior Acute Kidney Injury: Rates and Rate Ratios

Outcome	**Colistin** n (rate/100 days)	**Control** n (rate/100 days)	**IRR** (95% CI)
Acute kidney injury			
End of follow up	57 (9.1)	14 (1.6)	5.7 (3.1-10.4)
72 hours	23 (8.6)	6 (2.1)	4.1 (1.7-10.2)

Analysis included 101 matched pairs IRR- incidence rate ratio; CI- confidence interval

Table S9. Analysis in Subgroup of Patients Free of Prior Acute Kidney Injury: Cumulative incidence and Risk Differences

Outcome	**Colistin** n (%)	**Control** n (%)	**Risk Difference*** (95% CI)
Acute kidney injury			
End of follow up	57 (56)	14 (14)	43 (31-54)
72 hours	23 (23)	6 (6)	17 (7-26)

Analysis included 101 matched pairs; *risk difference expressed as percentage; CI- confidence interval

Table S10. Outcomes in patients with Acute Kidney Injury[a]

Outcome	**Colistin** n=77 AKI cases	**Control** n=33 AKI cases	**Difference (95%CI)**
AKI resolution	34 (44%)	19 (58%)	-13.5 (-33.6, 6.7)
Survival to discharge	30/34 (88%)	17/19 (89%)	-1 (-18.7, 16.3)
Persistent AKI	43 (56%)	14 (42%)	13.5 (-6.7, 33.6)
Survival to discharge	23/43 (53%)	9/14 (64%)	-10.8 (-39.9, 18.4)

a- survival was higher in patients with AKI recovery in both groups: colistin (88% vs. 53%, p=0.001); control (89% vs. 42%, p=0.08).

Figure S.1. Time to Acute kidney injury in the sub-group of patients without prior acute kidney injury

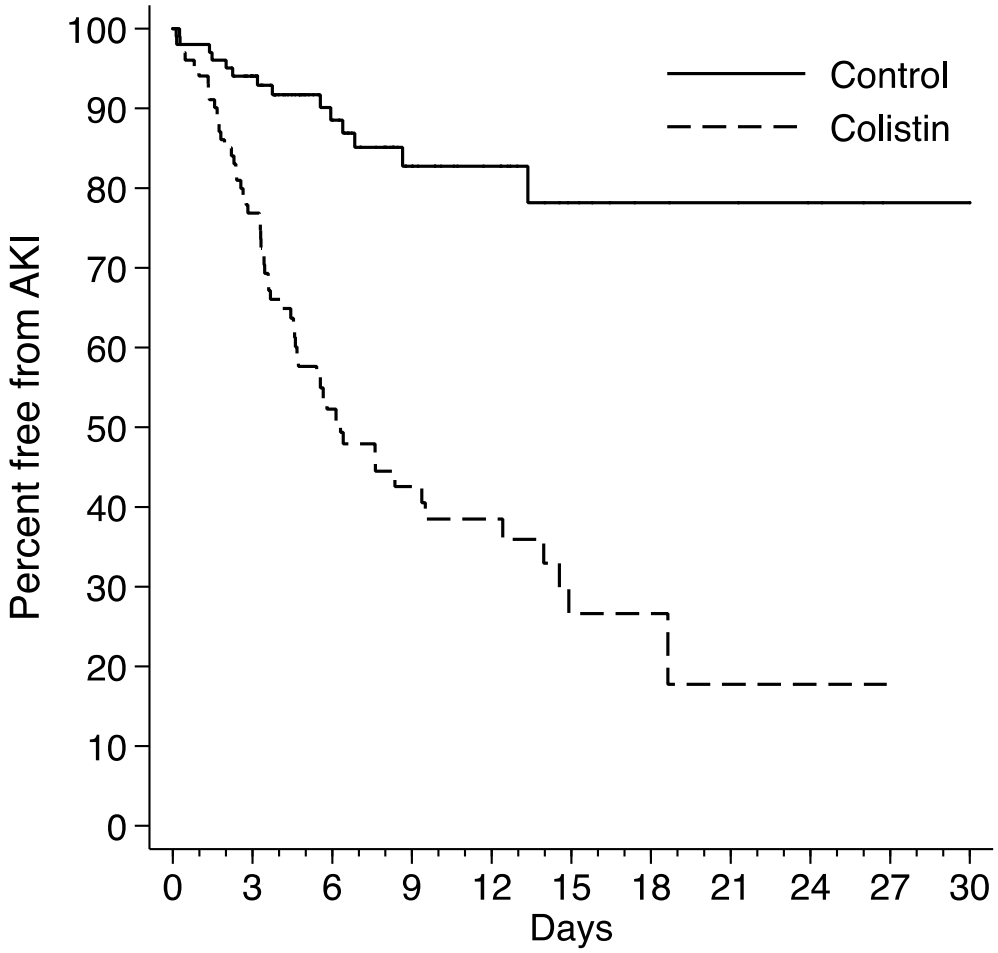
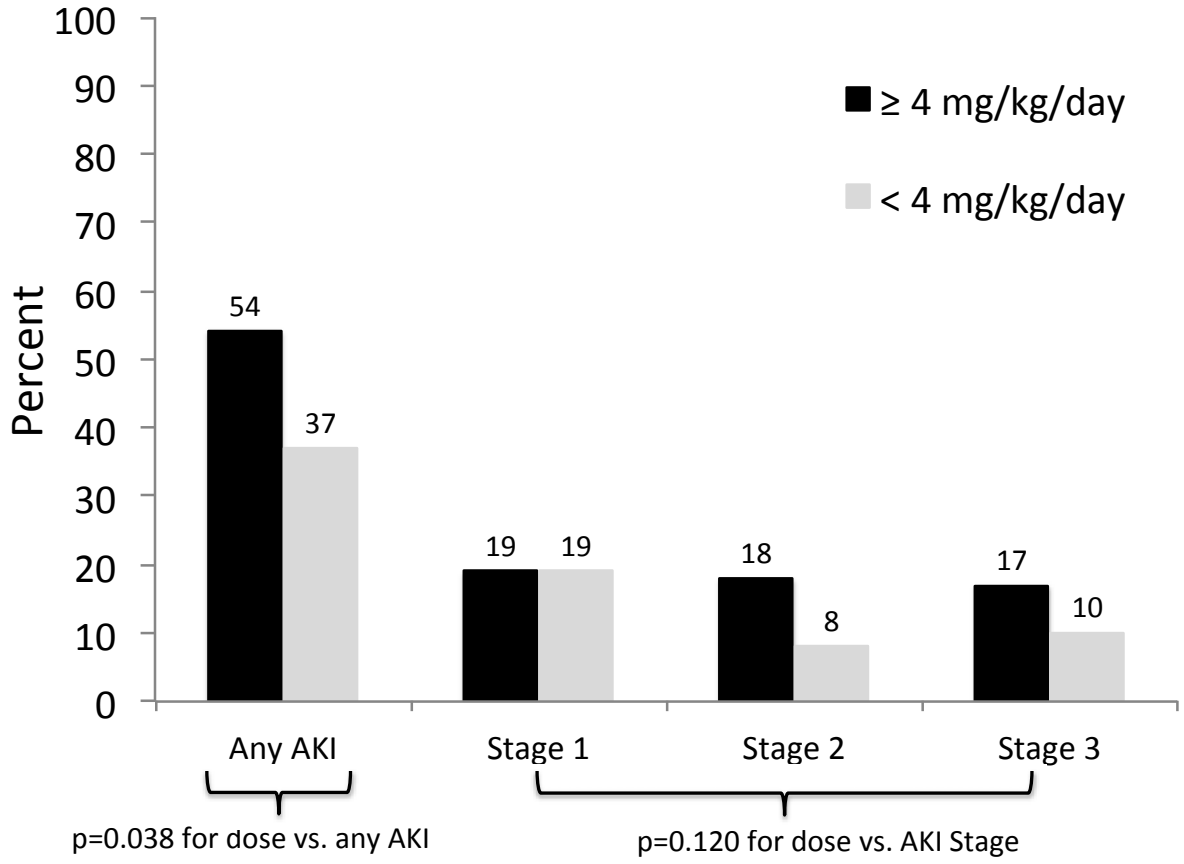


Figure S2. AKI in colistin exposed patients, stratified by colistin dose (mg/kg/day)



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