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Supplementary Materials

Table 1: List of Antibiotics

Amikacin	Cefepime	Ciprofloxacin	Gentamicin	Nafcillin	Tigecycline
Amoxicillin	Cefotaxime	Clarithromycin	Imipenem	Nitrofurantoin	Tobramycin
Ampicillin	Cefoxitin	Clindamycin	Levofloxacin	Oxacillin	Vancomycin
Azithromycin	Ceftazidime	Dalfopristin	Linezolid	Penicillin	
Aztreonam	Ceftriaxone	Daptomycin	Meropenem	Piperacillin/ Tazobactam	
Cefazolin	Cefuroxime	Doxycycline	Metronidazole	Rifampin	
Cefdinir	Cephalexin	Ertapenem	Moxifloxacin	Ticarcillin	

Table 2: List of Nephrotoxins (excluding antibiotics)

Acyclovir	Carboplatin	Ethacrynic Acid	Indomethacin	Methotrexate	Topiramate
Ambisome	Cidofovir	Foscarnet	Ketorolac	Naproxen	Triamterene
Amiloride	Cisplatin	Furosemide	Lisinopril	Phenytoin	Valacyclovir
Amphotericin B	Colistimethate	Ganciclovir	Lithium	Sirolimus	Valganciclovir
Aspirin	Cyclosporine	Hydrochlorothiazide	Mannitol	Spironolactone	Zonisamide
Bumetanide	Enalapril	Ibuprofen	Meloxicam	Sulfasalazine	
Captopril	Enalaprilat	Ifosfamide	Mesalamine	Tacrolimus	

Table 3: Characteristics of Included versus Excluded Patient Encounters

	Included N=5686	Excluded N=7120	p-value
Age (Years) Median (Q1-Q3)	3.92 (1.08-11.33)	6.92 (2.42-15.25)	<0.001
Males, N (%)	3256 (57.3%)	4029 (56.6%)	0.44
Race, N (%)			0.004
Caucasian	4568 (80.3%)	5580 (78.4%)	
African-American	872 (15.3%)	1246 (17.5%)	
Other	246 (4.3%)	294 (4.1%)	
Heart Failure, N (%)	343 (6%)	225 (3.2%)	<0.001
Liver Failure, N (%)	120 (2.1%)	94 (1.3%)	<0.001
Non-Renal Transplant, N (%)	246 (4.3%)	595 (8.4%)	<0.001
Malignancy, N (%)	360 (6.3%)	264 (3.7%)	<0.001
Suspected Bacterial Sepsis, N (%)	1602 (28.2%)	1104 (15.5%)	<0.001
Within first 24 hours of ICU admission			
Chronic Kidney Disease, N (%)	49 (0.9%)	128 (1.8%)	<0.001
Congenital Heart Disease, N (%)	996 (17.5%)	697 (9.8%)	<0.001
Epilepsy/Seizures, N (%)	1164 (20.5%)	1058 (14.9%)	<0.001
Baseline Serum Creatinine, Mean (SD)	0.37 mg/dL (0.24)	0.56 mg/dL (0.99)	<0.001
Major Surgery, N (%)	2415 (42.5%)	2016 (28.3%)	<0.001
Cardiopulmonary Bypass, N (%)	615 (10.8%)	386 (5.4%)	<0.001
Severe Anemia, N (%)	993 (17.5%)	684 (9.6%)	<0.001
Thrombocytopenia, N (%)	1360 (23.9%)	958 (13.5%)	<0.001
Hypoalbuminemia, N (%)	1213 (21.3%)	693 (9.7%)	<0.001
ePIM-2 Risk of Mortality Median (Q1-Q3)	1% (0-4%)	0.8% (0-1%)	<0.001
Vasopressor Use, N (%)	1503 (26.4%)	1059 (14.9%)	<0.001
Mechanical Ventilation, N (%)	2595 (45.6%)	2041 (28.7%)	<0.001
Within first 24 hours of ICU admission			
Hospital Mortality, N (%)	98 (1.7%)	105 (1.5%)	0.26
Length of ICU Stay in days, Median (Q1-Q3)	4 (2-8)	2 (1-3)	<0.001

Length of Hospital Stay in days, Median (Q1- Q3)	8 (5-14)	3 (2-5)	<0.001
ICU, intensive care unit ePIM2, electronic Pediatric Index of Mortality 2 SD, standard deviation Suspected Bacterial Sepsis: Ordering of blood cultures and a new antibiotic within 24 hours of each other Severe Anemia: Children < 5 years, Hemoglobin < 7 g/dL on two consecutive occasions; Children \geq 5 years, Hemoglobin < 8 g/dL on two separate occasions Thrombocytopenia: Platelet count < $150 \times 10^9/L$ on two consecutive occasions Hypoalbuminemia: Albumin level < 3 g/dL on two consecutive occasions			

Table 4: Sensitivity Analysis of Individual Medications, Multivariable Logistic Regression for AKI

Exposure	Adjusted OR, Stage 2/3 AKI (95% CI)	Adjusted OR, Stage 1/2/3 AKI (95% CI)
Cefazolin	0.90 (0.71-1.15)	n/a
Cefepime	1.12 (0.80-1.58)	1.17 (0.91-1.52)
Levofloxacin	2.15 (0.67-6.92)	2.39 (1.10-5.23)
Meropenem	n/a	0.40 (0.22-0.72)
Metronidazole	0.93 (0.58-1.49)	n/a
Piperacillin/Tazobactam	1.54 (1.22-1.94)	1.70 (1.42-2.05)
Rifampin	1.94 (0.56-6.71)	n/a
Tobramycin	1.28 (0.76-2.17)	1.17 (0.78-1.75)
Vancomycin	0.89 (0.69-1.13)	0.86 (0.70-1.04)
Age	1.01 (0.99-1.02)	1.05 (1.03-1.06)
Heart Failure	1.43 (1.00-2.04)	1.39 (1.03-1.88)
Liver Failure	1.35 (0.82-2.22)	1.54 (1.00-2.36)
Chronic Kidney Disease	2.14 (0.92-4.96)	2.11 (1.11-4.03)
Malignancy	0.56 (0.35-0.88)	n/a
Seizures/Epilepsy	1.30 (1.02-1.66)	1.24 (1.03-1.50)
Severe Anemia	1.24 (0.96-1.60)	1.11 (0.90-1.37)
Thrombocytopenia	1.65 (1.30-2.12)	1.29 (1.09-1.54)
Hypoalbuminemia	1.38 (1.11-1.71)	1.25 (1.03-1.53)
ePIM2 Score	n/a	1.02 (0.96-1.09)
Vasopressor Use	n/a	1.09 (0.89-1.34)
Mechanical Ventilation	1.54 (1.27-1.86)	1.21 (1.01-1.45)
Exposure to ≥ 3 Nephrotoxins	1.32 (0.92-1.91)	1.33 (1.01-1.77)
Suspected Bacterial Sepsis	1.71 (1.31-2.24)	1.45 (1.24-1.69)
OR, odds ratio CI, confidence interval ePIM2, electronic Pediatric Index of Mortality 2		

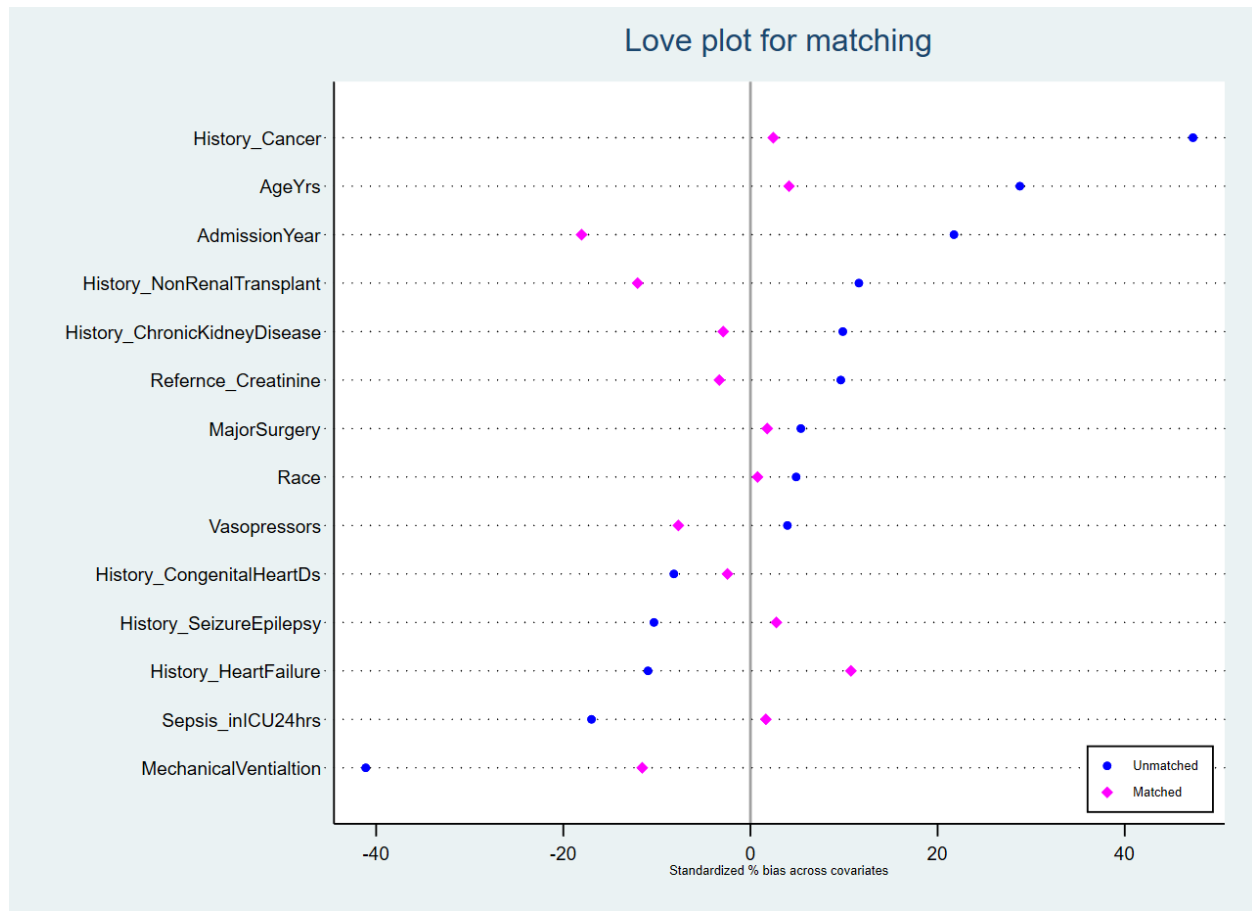
The sensitivity analysis used the same statistical methodology as the primary analysis, but compared stage 0 to stage 1, 2, or 3 AKI (whereas the primary analysis compared stage 0 or 1 AKI to stage 2 or 3 AKI). As with the primary analysis, all variables were assessed for univariate significance level of 0.2 followed by variable selection using LASSO regularization (least absolute shrinkage and selection operator). After clinical assessment in the final step, adjusted multivariate logistic regression for binary outcomes was performed to derive model inferences. All variables in the final model were considered significant at the 0.05 level. Model fit was tested using Hosmer-Lemeshow methodology and discriminative ability. The model comparing stage 0 to stages 1, 2, or 3 had appropriate fit and adequate discrimination (AUC 0.67).

Table 5: Multivariable Regularization Logistic Regression for Development of Stage 2/3 AKI in Patients Exposed to TZP versus Cefepime

Exposure	aOR (95% CI)	p-value
TZP vs. Cefepime	1.33 (0.92-1.94)	0.14
Cefazolin	1.19 (0.72-1.95)	0.50
Levofloxacin	1.72 (0.35-8.47)	0.51
Metronidazole	0.73 (0.40-1.32)	0.30
Rifampin	0.87 (0.21-3.51)	0.84
Tobramycin	0.99 (0.56-1.75)	0.97
Vancomycin	0.92 (0.63-1.35)	0.66
Age	1.01 (0.98-1.04)	0.58
Heart Failure	1.44 (0.89-2.34)	0.14
Liver Failure	1.50 (0.64-3.55)	0.35
Malignancy	0.53 (0.26-1.06)	0.07
Chronic Kidney Disease	1.02 (0.44-2.37)	0.96
Seizures/Epilepsy	1.38 (0.95-2.01)	0.09
Suspected Bacterial Sepsis	1.60 (0.88-2.88)	0.12
Severe Anemia	1.09 (0.77-1.54)	0.65
Thrombocytopenia	1.75 (1.15-2.66)	0.01
Hypoalbuminemia	1.29 (0.96-1.71)	0.09
Exposure to ≥ 3 Nephrotoxins	1.33 (0.82-2.16)	0.26
Mechanical Ventilation	2.19 (1.49-3.23)	< 0.001
aOR, adjusted odds ratio CI, confidence interval TZP, piperacillin/tazobactam		

As with the primary analyses, all variables in this additional analysis were assessed for univariate significance level of 0.2 followed by variable selection using LASSO regularization (least absolute shrinkage and selection operator). After clinical assessment in the final step, adjusted multivariate logistic regression for binary outcomes was performed to derive model inferences. All variables in the final model were considered significant at the 0.05 level. Model fit was tested using Hosmer-Lemeshow methodology and discriminative ability. This model had appropriate fit and adequate discrimination (AUC 0.68).

Figure 1: Love Plot and Details of Propensity Score Model



In order to account for indication bias, we performed propensity score-matched analysis. We matched the vancomycin plus cefepime group with vancomycin plus piperacillin-tazobactam group using propensity score on a 1:1 nearest neighbor matching without replacement creating 265 pairs. The variables used in the model for propensity score estimation included age, year of hospital admission, sex, race, heart failure, chronic kidney disease, non-renal transplant, malignancy, seizure/epilepsy, congenital heart disease, mechanical ventilation, major surgery, reference creatinine, suspected bacterial sepsis, and use of vasopressors. Matches were created without replacement using computational geometry based on distance between propensity scores (caliper 0.025). The analysis was carried out using STATA 15.1 using module "PSMATCH2".