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Incidence of acute kidney injury (AKI) and its impact on patient outcomes among adult hospitalized patients with carbapenem-resistant Gram-negative infections who received targeted treatment with a newer β-lactam or β-lactam/β-lactamase inhibitor-, polymyxin- or aminoglycoside-containing regimen

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Background: Limited comparative data exist on acute kidney injury (AKI) risk and AKI-associated outcomes in hospitalized patients with carbapenem-resistant Gram-negative infections (CR-GNIs) treated with a newer β-lactam/β-lactam-β-lactamase inhibitor (BL/BL-BLI)-, polymyxin (PB)- or aminoglycoside (AG)-containing regimen. This study quantified the risk of AKI and AKI-related outcomes among patients with CR-GNIs treated with a newer BL/BL-BLI-, PB- or AG-containing regimen.

Methods: A multicentre, retrospective, observational study was performed (2016–20). The study included adult hospitalized patients with (i) baseline estimated glomerular filtration rates ≥30 mL/min/1.73 m^2; (ii) CR-GN pneumonia, complicated urinary tract infection or bloodstream infection; and (iii) receipt of newer BL/BL-BLI, PG or AG within 7 days of index CR-GN culture for ≥3 days. Outcomes included AKI, in-hospital mortality and hospital costs.

Results: The study included 750 patients and most (48%) received a newer BL/BL-BLI. The median (IQR) treatment duration was 8 (5–11), 5 (4–8) and 7 (4–8) days in the newer BL/BL-BLI group, AG group and PB group, respectively. The PB group had the highest adjusted AKI incidence (95% CI) (PB: 25.1% (15.6%–34.6%) versus AG: 8.9% (5.7%–12.2%) versus newer BL/BL-BLI: 11.9% (8.1%–15.7%); $P=0.001$). Patients with AKI had significantly higher in-hospital mortality (AKI: 18.5% versus 'No AKI': 5.6%; $P=0.001$) and mean hospital costs (AKI: $49 192 versus 'No AKI': $38,763; $P=0.043$).

Conclusions: The AKI incidence was highest among PB patients and patients with AKI had worse outcomes. Healthcare systems should consider minimizing the use of antibiotics that augment AKI risk as a measure to improve outcomes in patients with CR-GNIs.

Introduction

Despite notable advances in patient care, it is estimated that approximately 1 in 25 hospitalized patients will develop a healthcare-associated infection and over half of infections will be resistant to a first-line treatment option.[1–4] While there has been a reduction in antibiotic-resistant Gram-positive infections in recent years,[4] the prevalence of carbapenem-resistant Gram-negative infections (CR-GNIs) has increased dramatically over the past decade among hospitalized patients worldwide.[5,6] Patients with CR-GNIs have extended hospital stays, higher mortality rates and greater healthcare costs compared with patients with serious carbapenem-susceptible GNIs.[7–13] As a testament to the importance of CR-GNIs, the WHO identified carbapenem-resistant *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and Enterobacterales as critical priority antibiotic-resistant pathogens that pose the greatest threat to human health.[14,15]

Several factors contribute to the increased morbidity and mortality among patients with CR-GNIs.[16–21] Patients with CR-GNIs are often critically ill and have multiple comorbidities.[16–21] One common comorbid condition among patients with CR-GNIs is renal disease.[22–31] Studies show that hospitalized patients with impaired renal function are at an increased risk of death and other healthcare-related problems relative to those without impaired renal function.[22–34] Additionally, data indicate that hospitalized patients who develop even modest cases of acute kidney injury (AKI), regardless of the cause, are at greater risk of unfavourable outcomes.[22–31,35] This is a critically important consideration for patients with CR-GNIs since potential agents include the polymyxins (PB) and aminoglycosides (AG), antibiotics with well-described renal adverse event profiles.[36–46] Although expert guidance documents have relegated AG and PB as last-line agents due their toxicity profiles,[47–49] they are still frequently used in many patients with CR-GNIs.[16,50]

While the deleterious consequences of AKI are well described across most therapeutic domains,[22–31,35,40,43,46] few comparative real-world evidence studies have compared the cumulative incidence of AKI between commonly used antibiotics among adult, hospitalized patients with serious CR-GNIs, and assessed the effects of treatment-associated AKI (overall and by baseline renal function status) on outcomes of patients with CR-GNIs.[39,41,46] Given these literature gaps, the objectives of this study were to quantify the incidence of AKI[51] and outcomes associated with AKI, overall and by presence of baseline renal impairment on index treatment day, among hospitalized adult patients with CR-GNIs who received targeted treatment with a newer β-lactam or β-lactam/β-lactamase inhibitor (newer BL/BL-BLI)-, PB- or AG-containing regimen.

Patients and methods

Study design and population

A retrospective, multicentre observational study of adult hospitalized patients in the PINC AI™ Healthcare Data (PHD),[52] between 2016 and 2020 was performed (Appendix A, available as Supplementary data at *JAC* Online). Patients from the PINC AI Healthcare Database were included in this study if they met the following criteria: (i) age ≥ 18 years; (ii) hospital discharge between 2016 and 2020; (iii) diagnosis for pneumonia (PNA), complicated urinary tract infection (cUTIs), or bloodstream infection (BSI) (Appendix B); (iv) presence of a CR-GN pathogen(s) other than carbapenem-resistant *A. baumannii* or *Stenotrophomonas maltophilia* on a clinical culture site consistent with infection diagnosis (index CR-GN culture day); (v) receipt of any antibiotic within −2 days to +3 days of the index CR-GN culture (Appendix C); (vi) receipt of a newer BL/BL-BLI- (i.e. ceftolozane/tazobactam, ceftazidime/avibactam, imipenem/relebactam, cefiderocol or meropenem/vaborbactam), AG (i.e. tobramycin, gentamicin or amikacin)- or PB (i.e. polymyxin B or colistin)-containing regimen within ≤7 days of the index CR-GN culture collection day (index treatment day); (vii) administration of a newer BL/BL-BLI -, AG- or PB-containing regimen for ≥3 days; (viii) serum creatinine (S_{CR}) data within ±2 days of admission; (ix) estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m^2 between −2 days to +2 days of the index treatment day; (x) ≥1 S_{CR} value(s) from +2 days post index treatment day through to +3 days after treatment discontinuation; (xi) no receipt of any renal replacement therapy (RRT) from −3 months to +2 days of the index treatment day; and (xii) no diagnosis of cystic fibrosis or moderate to severe bronchiectasis.

For patients who received a newer BL/BL-BLI, AG or PB within ≤7 days of the index CR-GN culture, the first treatment received for ≥3 days defined the treatment group. Patients were excluded if they received multiple treatments of interest (e.g. both AG and newer BL/BL-BLI) on the same index day for ≥3 days or if carbapenem-resistant *A. baumannii* or *S. maltophilia* was identified on the index CR-GN culture. We excluded patients with a carbapenem-resistant *A. baumannii* or *S. maltophilia* given the limited microbiological activity of approved newer BL/BL-BLI agents during the study period against these pathogens. Finally, only the first encounter was considered among patients with ≥1 hospital admissions that met the study criteria during the study period. Because this study utilized an already existing Health Insurance Portability and Accountability Act (HIPAA)-compliant fully de-identified data, it was exempt from Institutional Review Board (IRB) review.[52]

Baseline data covariates

Hospital-level variables included region, population served, teaching status and hospital size. Patient-level variables included information on demographics, medical history, hospitalization course, infection characteristics, renal function and medications received. Patient demographics included age, sex, race, primary payer and admission source. Medical history included hospitalization within ≤6 months of index admission and Charlson comorbidity index (CCI) (overall score and individual conditions).[53] Data collected during the hospital course included hospital length of hospitalization prior to the index CR-GN culture collection day, residence in an ICU on the index CR-GN culture day, and receipt of mechanical ventilation (MV) on the index CR-GN culture day. Infection characteristics included CR-GN pathogen(s) on the index culture and infection type(s). Renal function was assessed using available S_{CR} and eGFR values [calculated with the modification of diet in renal disease (MDRD) equation[54]] recorded from admission through to 3 days after newer BL/BL-BLI, AG or PB discontinuation. Antibiotic(s) received between admission and the index treatment day, duration of newer BL/BL-BLI, AG or PB treatment, other antibiotics received from the index treatment allocation day through to 3 days after newer BL/BL-BLI, AG or PB discontinuation, and renal-toxic medications (Appendix D) received between admission and the end of treatment with a newer BL/BL-BLI, AG or PB were included to capture patient medication use.

Outcomes

The AKI outcomes were treatment-associated AKI and receipt of any RRT. Treatment-associated AKI incidence proportions (i.e. cumulative incidence) were based on the risk, injury, and failure components of the risk of renal dysfunction, injury to kidney, failure or loss of kidney function, and end-stage kidney disease (RIFLE) criteria[51] and it was assessed from Day 2 of newer BL/BL-BLI, AG or PB treatment through to 3 days after newer BL/BL-BLI, AG or PB discontinuation. The following RIFLE classifications were evaluated: (i) RIFLE risk (≥1.5 times increase in index treatment day S_{CR}); (ii) RIFLE injury (≥2 times increase in index treatment day S_{CR}); and (iii) RIFLE failure (≥3 times increase in index treatment day S_{CR} or S_{CR} ≥ 4.0 mg/dL).[51] Receipt of any RRT was assessed from the index treatment day to hospital discharge. Clinical outcomes included 30 day mortality, in-hospital mortality, in-hospital mortality or discharge to hospice, and discharge destination (home versus other). Healthcare resource utilization (HRU) outcomes evaluated were hospital length of stay (LOS) from the index treatment day to hospital discharge, hospital costs from the index treatment day to hospital discharge, and 30 day hospital readmissions among survivors.

Statistical methods

Two sets of analyses were performed. We first compared baseline covariates and AKI outcomes between the three treatment groups. As part of

the treatment–AKI outcome analyses, we evaluated the association between AKI outcomes and treatment by eGFR at the initiation of treatment (≥60 versus <60 mL/min/1.73 m^2). Restricted analyses were also performed in the newer BL/BL-BLI subset to assess the associations between (i) AKI outcomes and treatment by receipt of AG/PB for ≥2 days during newer BL/BL-BLI treatment and (ii) AKI outcomes and each newer BL/BL-BLI received. Second, we compared baseline variables and clinical/HRU outcomes between patients who experienced AKI, defined by RIFLE, relative to those who did not.

We conducted unadjusted statistical inferences for each set of analyses. The Student's *t*-test was used to compare means between two groups (e.g. AKI versus 'No AKI'), a one-way ANOVA was used to compare means between more than two groups (e.g. the three treatment groups) and the Kruskal–Wallis test was used to compare continuous distributions non-parametrically between two or more groups. The chi-squared test was used to compare frequencies by groups unless a cell count was <5, wherein the Fisher exact test was used. Kaplan–Meier survival curves were used to compare the time to AKI between treatment groups. We compared survivor functions of the three treatment groups with the log-rank test.

Multivariable regression models were then developed to examine the associations between (i) treatment and occurrence of AKI (risk component of RIFLE criteria) and (ii) occurrence of AKI and clinical/HRU outcomes.[51] Logistic regression was used to examine binary outcomes. Generalized linear models with a logarithmic link and a gamma distribution were used to examine continuous outcomes due to the skewed distributions of these outcomes. Inverse probability of weighting (IPW)[55,56] was then used to evaluate the associations between the occurrence of AKI (risk component of RIFLE criteria[51]) and the clinical and economic outcomes, while adjusting for potential baseline confounding variables. For the propensity score model, clinically plausible confounders were selected *a priori* for adjustment (Appendix E).[57] When constructing the propensity model, collinearity was assessed between potential predictors using correlation statistics and the variance inflation factor. As a sensitivity analysis, we also developed multivariable regression models to examine the association between the occurrence of AKI (risk component of RIFLE criteria)[51] and the clinical and economic outcomes while adjusting for clinically plausible confounders (Appendix E). All analyses were done using Stata/MP 17.0 for Windows (StataCorp LLC, College Station, TX, USA). *P* values of <0.05 were considered statistically significant.

Results

During the study period, 750 patients met the study criteria (Table S1). Among the 750 patients, 48% received a newer BL/BL-BLI, 39% received an AG and 19% received a PB. The median (IQR) treatment duration was 8 days (5–11) in the newer BL/BL-BLI group, 5 (4–8) days in the AG group and 7 (4–8) days in the PB group. In the newer BL/BL-BLI group, most patients either received ceftolozane/tazobactam (60.6%) or ceftazidime/avibactam (35.2%). Tobramycin (60.4%), followed by gentamicin (25.3%) were the most frequently administered AG, while 96.8% of patients in the PB group received colistin. The median (IQR) and mean (SD) number of days with S_{CR} values per patient Day 2 of newer BL/BL-BLI, AG or PB treatment through to 3 days after newer BL/BL-BLI, AG or PB discontinuation were 5 (2–8) and 6.4 (6.5) mg/dL, respectively. Table 1 presents comparisons of baseline characteristics between treatment groups. All hospital-level variables were significantly different between treatment groups. For patient-level variables, treatment groups were significantly different with regard to mean age, sex, certain comorbid conditions, CR-GN pathogen, infection type, eGFR at admission and on the index treatment day, other antibiotics received prior to the index treatment day and during treatment, and concurrent receipt of other nephrotoxins. Among the baseline variables that were significantly different between treatment groups, infection type and concurrent treatment with a tetracycline-like antibiotic (i.e. receipt of doxycycline, eravacycline, minocycline, omadacycline, tetracycline and/or tigecycline) were the only ones that were significantly associated with AKI (defined by RIFLE risk criteria).

Unadjusted treatment–AKI outcome comparisons are shown in Table 2. In the overall bivariate analyses, significant associations were noted between treatment and AKI by RIFLE risk (PB: 23.4% versus AG: 10.6% versus newer BL/BL-BLI: 10.5%; $P = 0.002$) and AKI by RIFLE injury (PB: 10.6% versus AG: 3.1% versus newer BL/BL-BLI: 5.2%; $P = 0.014$). No significant differences between treatment and RIFLE failure and receipt of RRT were observed. Similar associations were observed between treatment and AKI outcomes within each eGFR category (Table 2). For all three treatment groups, patients who experienced AKI (RIFLE risk) had longer treatment durations relative to those who did not experience AKI (Figure S1). For patients in the newer BL/BL-BLI group who received PB for ≥2 days ($n = 15$), 5 (33%) developed AKI (RIFLE risk) versus 9.5% (33 out of 38) who received neither PB nor AG concurrently (Table S2). No differences in AKI outcomes were observed within the newer BL/BL-BLI treatments (Table S3). Eighteen patients (22.8%) in the PB group received a newer BL/BL-BLI. Among those who received a newer BL/BL-BLI, the incidence of AKI was 16.7% (3/18). Among those who did not receive a newer BL/BL-BLI, the incidence of AKI was 25.0% (19/76). The *P* value comparing the two AKI incidence proportions was $P = 0.550$.

Comparison of the Kaplan–Meier time-to-AKI (RIFLE risk) curves between treatment groups (overall and by eGFR category on the index treatment day) are shown in Figure 1. In the Kaplan–Meier analyses (Figure 1), significant differences in time to AKI (RIFLE risk) between treatment groups were observed overall and within each eGFR category ($P < 0.001$ for each plot). Results of the adjusted treatment–AKI (RIFLE risk) logistic regression analyses are shown in Figure 2. Consistent with the unadjusted analyses, patients in the PB group had the highest adjusted AKI incidence (95% CIs) of RIFLE risk overall: PB: 25.1% (15.6%–34.6%) versus AG: 8.9% (5.7%–12.2%) versus newer BL/BL-BLI: 11.9% (8.1%–15.7%); $P = 0.001$.

Unadjusted and IPW comparisons of clinical and HRU outcomes between patients who experienced AKI (RIFLE risk) relative to those who did not experience AKI are shown in Table 3. Patients with AKI had higher incidences of mortality, and increased hospital LOS and hospital costs compared with patients who did not experience AKI (RIFLE risk). No differences were noted by AKI status with regard to discharge destination (home versus other) or 30 day readmissions. Results of the multivariable regression analyses that examined the association between AKI (risk component of RIFLE criteria) and the study outcomes were consistent with the IPW comparisons (Table S4).

Discussion

In this study of adult hospital patients with CR-GNIs at high risk for AKI due to their underlying disease severity, comorbidities

Table 1. Baseline stratified by treatment group and presence or absence of AKI defined by risk in RIFLE criteria[51]

	Newer BL/BL-BLI $N=363$	AG $N=293$	PB $N=94$	*P* value	No AKI $N=659$	AKI $N=91$	*P* value
Census region							
Midwest	96 (26.5)	40 (13.7)	9 (9.6)		131 (19.9)	14 (15.4)	
Northeast	52 (14.3)	21 (7.2)	19 (20.2)		81 (12.3)	11 (12.1)	
South	212 (58.4)	227 (77.5)	66 (70.2)	<0.001	440 (66.8)	65 (71.4)	0.747
West	3 (0.8)	5 (1.7)	0 (0)		7 (1.1)	1 (1.1)	
Number of beds							
<300	86 (23.7)	118 (40.3)	25 (26.7)		203 (30.1)	26 (28.6)	
300 to 499	117 (32.2)	92 (31.4)	40 (42.6)	<0.001	212 (32.2)	37 (40.7)	0.255
500+	160 (44.1)	83 (28.3)	29 (30.9)		244 (37.0)	28 (30.8)	
Teaching hospital	203 (55.9)	84 (28.7)	51 (54.3)	<0.001	302 (45.8)	36 (39.6)	0.312
Urban location of hospital	331 (91.2)	234 (79.9)	76 (80.9)	<0.001	566 (85.9)	75 (82.4)	0.379
Mean age, years (SD)	63.3 (15.4)	60.2 (16.9)	56.6 (18.3)	<0.001	61.3 (16.6)	60.7 (16.0)	0.753
Sex: male	243 (66.7)	170 (58.0)	65 (69.1)	0.031	421 (63.9)	57 (62.6)	0.817
Race							
White	263 (72.4)	221 (75.4)	66 (70.2)		489 (74.2)	61 (67.0)	
Black	68 (18.7)	46 (15.7)	14 (14.9)	0.330	117 (17.8)	11 (12.1)	0.001
Other	26 (7.2)	24 (8.2)	11 (11.7)		43 (6.5)	18 (19.8)	
Unknown	6 (1.7)	2 (0.7)	3 (3.2)		10 (1.5)	1 (1.1)	
Admission source							
Non-healthcare facility (including home)	264 (72.7)	217 (74.1)	68 (72.3)		481 (73.0)	68 (74.7)	
Clinic	16 (4.4)	19 (6.5)	1 (1.1)	0.369	35 (5.3)	1 (1.1)	
Transfer from SNF, ICF	34 (9.4)	22 (7.5)	7 (7.5)		58 (8.8)	5 (5.5)	0.115
Transfer from another non-acute care facility or other/unknown	49 (13.5)	35 (12.0)	18 (19.2)		85 (12.9)	17 (18.7)	
Insurance							
Medicare	244 (67.2)	172 (58.7)	61 (65.0)		414 (62.8)	63 (69.2)	
Medicaid	60 (16.5)	63 (21.5)	21 (22.3)		129 (19.6)	15 (16.5)	
Managed care	42 (11.6)	33 (11.3)	6 (6.4)	0.067	72 (10.9)	9 (9.9)	0.876
Commercial/Worker's Comp/ Self-Pay	11 (3.0)	14 (4.8)	6 (6.4)		28 (4.3)	3 (3.3)	
Other	6 (1.7)	11 (3.8)	0 (0)		16 (2.4)	17 (18.7)	
Hospitalization in 6 months prior to index CR-GN admission	141 (34.9)	99 (32.0)	33 (34.7)	0.393	245 (37.2)	28 (30.8)	0.234
CCI score							
Mean (SD)	3.2 (2.3)	2.9 (2.1)	2.8 (2.1)	0.219	2 (1–4)	3 (2–5)	0.004
Median (IQR)	3 (2–4)	2 (1–4)	2 (1–4)	0.338	2.9 (2.2)	3.6 (2.3)	0.006
Charlson comorbidities							
Acute myocardial infarction	51 (14.1)	30 (10.2)	14 (14.9)	0.271	77 (11.7)	18 (19.8)	0.030
Congestive heart failure	118 (32.5)	93 (31.7)	17 (18.1)	0.021	194 (29.4)	34 (37.4)	0.123
Peripheral vascular disease	41 (11.3)	23 (7.9)	11 (11.7)	0.289	58 (8.8)	17 (18.7)	0.003
Cerebrovascular disease	45 (12.4)	40 (13.7)	11 (11.7)	0.842	84 (12.8)	12 (13.2)	0.906
Dementia	46 (12.7)	36 (12.3)	8 (8.5)	0.532	78 (11.8)	12 (13.2)	0.710
COPD	118 (32.5)	144 (49.2)	43 (45.7)	<0.001	258 (39.2)	47 (51.7)	0.023
Rheumatoid disease	12 (3.3)	8 (2.7)	3 (3.2)	0.914	20 (3.0)	3 (3.3)	0.752
Peptic ulcer disease	10 (2.8)	7 (2.4)	1 (1.1)	0.754	16 (2.4)	2 (2.2)	1.000
Mild liver disease	14 (3.9)	22 (7.5)	6 (6.4)	0.122	36 (5.5)	6 (6.6)	0.660
Diabetes	94 (25.9)	61 (20.8)	27 (28.7)	0.180	157 (23.8)	25 (27.5)	0.447
Diabetes with complications	67 (18.5)	42 (14.3)	6 (6.4)	0.013	99 (15.0)	17 (18.7)	0.344
Hemiplegia or paraplegia	70 (19.3)	48 (16.4)	19 (20.2)	0.552	118 (17.9)	19 (20.9)	0.491

Continued

Table 1. *Continued*

	Newer BL/BL-BLI $N=363$	AG $N=293$	PB $N=94$	*P* value	No AKI $N=659$	AKI $N=91$	*P* value
Renal disease	83 (22.9)	45 (15.4)	14 (14.9)	0.029	119 (18.1)	23 (25.3)	0.100
Cancer	22 (6.1)	20 (6.8)	6 (6.4)	0.924	41 (6.2)	7 (7.7)	0.591
Moderate/severe liver disease	5 (1.4)	6 (2.1)	3 (3.2)	0.416	12 (1.8)	2 (2.2)	0.683
Metastatic cancer	16 (4.4)	10 (3.4)	3 (3.2)	0.803	27 (4.1)	2 (2.2)	0.563
AIDS	2 (0.6)	2 (0.7)	1 (1.1)	0.687	4 (0.6)	1 (1.1)	0.477
LOS prior to index CR-GN culture, days							
Mean (SD)	5.8 (10.7)	6.7 (13.0)	6.7 (10.6)	0.501	5.8 (10.5)	9.6 (17.6)	0.003
Median (IQR)	1 (1–5)	1 (1–6)	2 (1–8)	0.109	1 (1–5)	2 (1–10)	0.001
Residence in ICU on index CR-GN culture day	146 (44.2)	112 (38.2)	45 (47.9)	0.252	256 (38.9)	47 (51.7)	0.020
MV on index CR-GN culture day	123 (33.9)	89 (20.4)	41 (43.6)	0.061	213 (32.3)	40 (44.0)	0.028
Carbapenem-resistant organisms on index culture							
Escherichia coli	12 (33.3)	9 (3.1)	3 (3.2)	1.000	19 (2.9)	5 (5.5)	0.185
Enterobacter aerogenes	0 (0)	0 (0)	0 (0)	1.000	0 (0)	0 (0)	1.000
Enterobacter cloacae	11 (3.0)	12 (4.1)	1 (1.1)	0.378	23 (3.5)	1 (1.1)	0.344
Klebsiella pneumoniae	73 (20.1)	25 (8.5)	27 (28.7)	<0.001	108 (16.4)	17 (18.7)	0.582
Klebsiella oxytoca	2 (0.6)	1 (0.3)	1 (1.1)	0.608	3 (0.5)	1 (1.1)	0.405
Morganella morganii	0 (0)	0 (0)	0 (0)	1.000	0 (0)	0 (0)	1.000
Proteus mirabilis	1 (0.3)	4 (1.4)	1 (1.1)	0.227	6 (0.9)	0 (0)	1.000
P. aeruginosa	251 (69.2)	228 (77.8)	59 (62.8)	0.006	477 (72.4)	61 (67.0)	0.288
Serratia marcescens	3 (0.8)	3 (1.0)	0 (0)	1.000	6 (0.9)	0 (0)	1.000
Other Gram negative	17 (4.7)	15 (5.1)	6 (6.4)	0.798	31 (4.7)	7 (7.7)	0.223
Number of CR-GN organisms in the index culture							
1	356 (98.1)	289 (98.6)	90 (95.7)		645 (97.9)	90 (98.9)	
2	7 (1.9)	4 (1.4)	4 (4.3)	0.210	14 (2.1)	1 (1.1)	1.000
3+	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	
Infection type							
HABP/VABP	214 (53.0)	203 (65.5)	75 (76.5)	<0.001	418 (63.4)	74 (81.3)	0.001
cUTI	146 (36.1)	102 (32.9)	22 (22.5)	0.008	246 (37.3)	24 (26.4)	0.041
BSI	80 (19.8)	34 (11.0)	21 (21.4)	<0.001	122 (18.5)	13 (14.3)	0.325
Number of CR-GN infection types							
1	290 (72.8)	249 (80.3)	70 (71.4)		537 (81.5)	72 (79.1)	
2	69 (17.1)	42 (13.6)	24 (24.5)	0.109	117 (17.8)	18 (19.8)	0.587
3	4 (1.0)	2 (0.7)	0 (0)		5 (0.8)	1 (1.1)	
eGFR at admission, mL/min/1.73 m^2							
Mean (SD)	68.8 (38.9)	70.5 (31.1)	87.6 (67.1)	<0.001	72.5 (41.3)	67.2 (30.9)	0.237
Median (IQR)	60.0 (51.8–81.0)	60.0 (60.0–85.0)	60.0 (60.0–110.0)	0.005	60 (57–88)	60 (53–81)	0.215
S_{CR} at admission, mg/dL							
Mean (SD)	1.1 (0.6)	0.9 (0.6)	1.0 (0.7)	0.067	1.0 (0.6)	1.0 (0.6)	0.872
Median (IQR)	0.9 (0.6–1.3)	0.8 (0.6–1.1)	0.8 (0.6–1.2)	0.115	0.8 (0.6–1.2)	0.8 (0.6–1.3)	1.000
eGFR on index treatment day							
Mean (SD)	75.1 (34.3)	78.4 (31.5)	106.9 (112.1)	<0.001	80.9 (53.2)	75.9 (33.8)	0.383
Median (IQR)	60.0 (59.5–90.0)	60.0 (60.0–94.0)	60.0 (60.0–113.0)	0.003	60 (60–94)	60 (60–90)	0.500
S_{CR} on index treatment day, mg/dL							
Mean (SD)	0.8 (0.4)	0.7 (0.3)	0.7 (0.4)	<0.001	0.8 (0.4)	0.7 (0.4)	0.059
Median (IQR)	0.8 (0.5–1.0)	0.7 (0.5–0.9)	0.6 (0.4–0.9)	0.003	0.7 (0.5–1.0)	0.6 (0.4–0.9)	0.026
Antibiotics received between admission and index treatment day							

Continued

Table 1. *Continued*

	Newer BL/BL-BLI N=363	AG N=293	PB N=94	P value	No AKI N=659	AKI N=91	P value
Aminoglycoside[a]	18 (5.0)	72 (24.6)	11 (11.7)	<0.001	88 (13.4)	13 (14.3)	0.807
β-Lactam (older)[b]	335 (92.3%)	273 (93.2)	91 (96.8%)	0.300	611 (92.7)	88 (96.7)	0.157
Fluoroquinolone	62 (17.1)	62 (21.2)	16 (17.0)	0373	122 (18.5)	18 (19.8)	0.771
Vancomycin	233 (64.2)	172 (58.7)	58 (61.7)	0.356	405 (61.5)	58 (63.7)	0.675
Daptomycin	10 (2.8)	7 (2.4)	6 (6.4)	0.132	18 (2.7)	5 (5.5)	0.152
Other glycopeptide/ glycopeptide-like agents[c]	0 (0)	0 (0)	0 (0)	1.000	0 (0)	0 (0)	1.000
Macrolide[d]	26 (7.2)	34 (11.6)	12 (12.8)	0.085	66 (10.0)	6 (6.6)	0.299
Oxazolidone	24 (6.6)	5 (1.7)	6 (6.4)	0.009	31 (4.7)	4 (4.4)	1.000
Polymyxin	2 (0.6)	4 (1.4)	17 (18.1)[e]	<0.001	18 (2.7)	5 (5.5)	0.184
Rifamycin	0 (0)	0 (0)	0 (0)	1.000	0 (0)	0 (0)	1.000
Sulpha-like agents[f]	9 (2.5)	10 (3.4)	2 (2.1)	0.741	19 (2.9)	2 (2.2)	1.000
Tetracycline-like agents[g]	22 (6.1)	21 (7.2)	7 (7.5)	0.809	40 (6.1)	10 (11.0)	0.078
Number of antibiotics received between admission and index treatment day							
0	13 (3.6)	15 (5.1)	4 (4.3)		30 (4.6)	2 (2.2)	
1	228 (62.8)	142 (48.5)	43 (45.7)		364 (55.2)	49 (53.9)	
2	97 (26.7)	100 (34.1)	33 (35.1)	0.012	198 (30.1)	32 (35.2)	0.595
3	19 (5.2)	28 (9.6)	11 (11.7)		53 (8.0)	5 (5.5)	
≥4	6 (1.7)	8 (2.7)	3 (3.2)		14 (2.1)	3 (3.3)	
Receipt of any of the other treatment allocations of interest from index treatment day through to 3 days after newer BL/BL-BLI, AG or PB discontinuation							
Newer BL/BL-BLI	NA	38 (13.0)	18 (22.8)	NA	46 (7.0)	10 (11.0)	0.173
AG	70 (19.3)	NA	11 (11.7)	NA	71 (10.8)	10 (11.0)	0.951
PB	19 (5.2)	18 (6.1)	NA	NA	29 (4.4)	8 (8.8)	0.070
Other antibiotics received from index treatment day through to 3 days after newer BL/BL-BLI, AG or PB discontinuation							
β-Lactam (older)[b]	268 (73.8)	242 (82.6)	79 (84.0)	0.009	520 (78.9)	69 (75.8)	0.502
Fluoroquinolone	41 (11.3)	66 (22.5)	12 (12.8)	<0.001	106 (16.1)	13 (14.3)	0.660
Vancomycin	163 (44.9)	126 (43.0)	39 (41.5)	0.795	279 (42.3)	49 (53.8)	0.038
Daptomycin	22 (6.1)	15 (5.1)	6 (6.4)	0.840	39 (5.9)	4 (4.4)	0.809
Other glycopeptide/ glycopeptide-like agents[c]	1 (0.3)	0 (0)	0 (0)	1.000	0 (0)	1 (1.1)	0.121
Macrolide[d]	14 (3.9)	17 (5.8)	6 (6.4)	0.409	33 (5.0)	4 (4.4)	1.000
Oxazolidone	28 (7.7)	16 (5.5)	5 (5.3)	0.448	41 (6.2)	8 (8.8)	0.352
Rifamycin	0 (0)	0 (0)	0 (0)	1.000	0 (0)	0 (0)	1.000
Sulpha-like agents[f]	13 (3.6)	13 (4.4)	3 (3.2)	0.833	28 (4.3)	1 (1.1)	0.240
Tetracycline-like agents[g]	32 (8.9)	24 (8.2)	18 (19.2)	0.005	58 (8.8)	16 (17.6)	0.008
Receipt of medications known to cause renal toxicity between admission and end of treatment with a newer BL/BL-BLI, AG or PB	331 (92.1)	293 (100)	80 (85.1)	<0.001	616 (93.5)	88 (96.7)	0.229

Continued

Table 1. *Continued*

	Newer BL/BL-BLI $N=363$	AG $N=293$	PB $N=94$	*P* value	No AKI $N=659$	AKI $N=91$	*P* value
Receipt of IV contrast media from index treatment day through to 3 days after newer BL/BL-BLI, AG or PB discontinuation	71 (19.6)	32 (10.9)	16 (17.0)	0.010	102 (15.5)	17 (18.7)	0.43

SNF, skilled nursing facility; ICF, intermediate care facility. All values are given as *n* (%) unless otherwise stated.
[a]Aminoglycosides included gentamicin, tobramycin and amikacin.
[b]Older β-lactams included amoxicillin/clavulanate, amoxicillin, ampicillin, ampicillin/sulbactam, aztreonam, bacampicillin, carbenicillin, cefaclor, cefadroxil, cefamandole, cefazolin, cefdinir, cefditoren pivoxil, cefepime, cefixime, cefonicid, cefoperazone, cefotaxime, cefotetan, cefoxitin, cefpodoxime, cefprozil, ceftaroline, ceftibuten, ceftizoxime, ceftriaxone, cefalexin, cefapirin, dicloxacillin, doripenem, ertapenem, imipenem, loracarbef, meropenem, mezlocillin, penicillin, piperacillin, piperacillin/tazobactam, ticarcillin/clavulanate and ticarcillin.
[c]Other glycopeptide/glycopeptide-like agents included dalbavancin, oritavancin and telavancin.
[d]Macrolides included azithromycin, clarithromycin, erythromycin/sulfisoxazole and quinupristin/dalfopristin.
[e]Mean time from start of PB from admission to index PB treatment day was 1.2 days (SD = 2.8); only two patients in the PB group received a PB for more than 1 day before the index day.
[f]Sulpha-like drugs included sulfamethoxazole, sulfamethoxazole/trimethoprim, trimethoprim and sulfisoxazole.
[g]Tetracycline-like drugs included doxycycline, eravacycline, minocycline, omadacycline and tigecycline.

Table 2. Unadjusted comparisons of AKI per RIFLE criteria[51] between treatment groups

	Newer BL/BL-BLI ($N=363$)	AG ($N=293$)	PB ($N=94$)	*P* value
Overall ($N=750$)				
RIFLE risk	38 (10.47)	31 (10.58)	22 (23.40)	0.002
RIFLE injury	19 (5.23)	9 (3.07)	10 (10.64)	0.014
RIFLE failure	5 (1.38)	3 (1.02)	4 (4.26)	0.090
Receipt of RRT	6 (1.65)	4 (1.37)	2 (2.13)	0.845
eGFR < 60 mL/min/1.73 m^2 on index treatment day ($n=160$)	$n=96$	$n=56$	$n=18$	
RIFLE risk	9 (9.38)	7 (15.22)	3 (16.67)	0.472
RIFLE injury	3 (3.13)	1 (2.17)	1 (5.56)	0.633
RIFLE failure	0 (0.00)	0 (0.00)	1 (5.56)	0.113
Receipt of any RRT	1 (1.04)	1 (2.17)	2 (11.11)	0.053
eGFR ≥ 60 mL/min/1.73 m^2 on index treatment day ($n=590$)	$n=267$	$n=247$	$n=76$	
RIFLE risk	29 (10.86)	24 (9.72)	19 (25.00)	0.001
RIFLE injury	16 (5.99)	8 (3.24)	9 (11.84)	0.016
RIFLE failure	5 (1.87)	3 (1.21)	3 (3.95)	0.262
Receipt of any RRT	5 (1.87)	3 (1.21)	0 (0.00)	0.693

All values are given as *n* (%). The following RIFLE classifications were evaluated: (1) RIFLE risk (increase in index treatment day S_{CR} by ≥1.5 times); (2) RIFLE injury (increase in index treatment day S_{CR} by ≥2 times); and (3) RIFLE failure (increase in index treatment day S_{CR} by ≥3 times, or S_{CR} ≥ 4.0 mg/dL).[51]

and concomitant receipt of other potentially nephrotoxic medications,[16–21] the adjusted AKI incidence[51] was considerably higher among patients who received a PB-containing regimen versus patients who received a newer BL/BL-BLI- or AG-containing regimen. The overall PB-associated AKI incidence proportion of 23.4% observed in this study was comparable or lower to the AKI proportions reported in other studies that assessed the incidence of nephrotoxicity among patients who received a PB intravenously.[36,39–41,43–46,58–63] In a systematic review of the estimated incidences of nephrotoxicity in patients treated with systemic PB, the observed nephrotoxicity incidence proportion among studies (103 studies: 21 451 patients) using the RIFLE criteria to define AKI was 38.8% (95% CI: 35.8%–42.0%).[41] Additionally, fewer PB patients in this study developed severe AKI relative to other studies.[36,41]

Several factors potentially contributed to the lower incidence of PB-associated AKI observed here. This study only included patients with eGFR ≥ 30 mL/min/1.73 m^2 at admission and was limited to the index CR-GNI episode during hospitalization. We also excluded patients who recently received any RRT or had an CR-GNI due to carbapenem-resistant *A. baumannii* or *S. maltophilia*. Consequently, few patients in the PB group

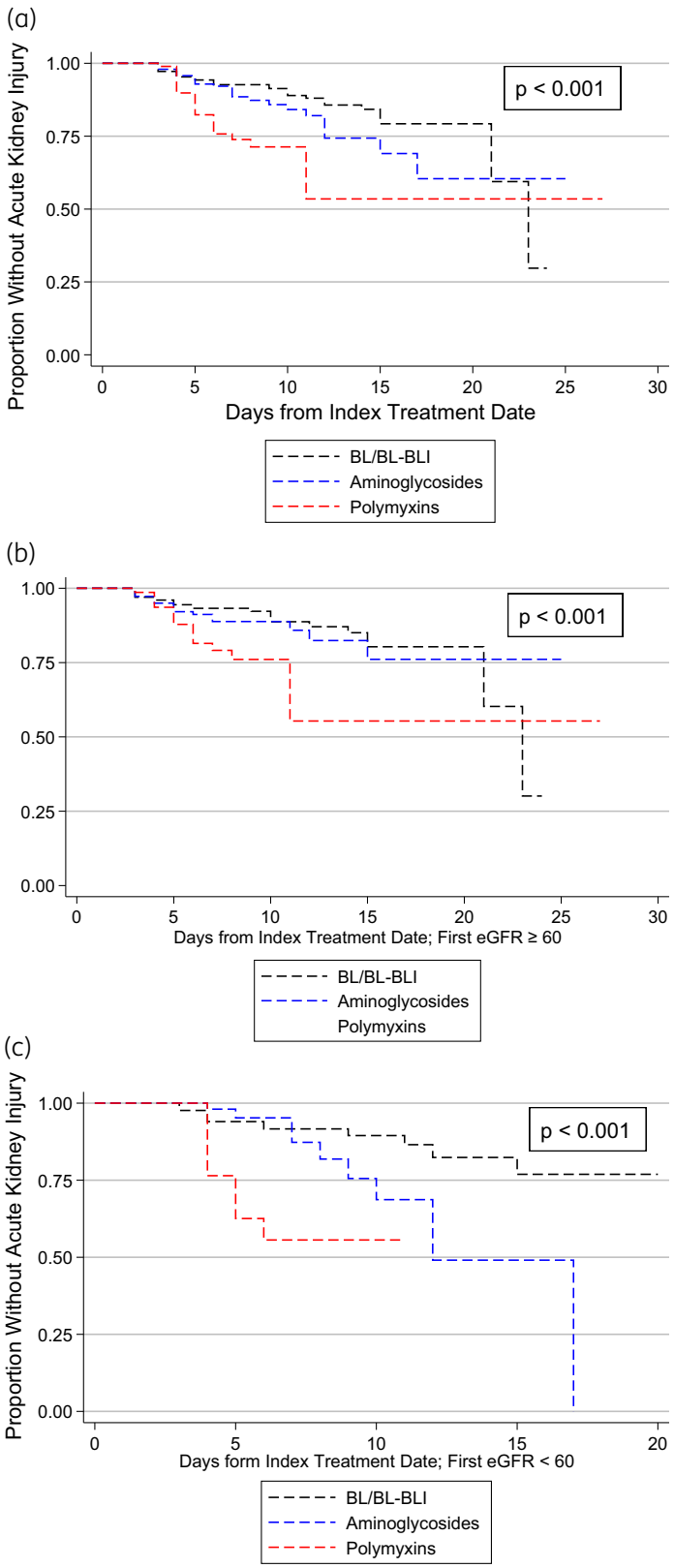

Figure 1. Time to treatment-associated AKI defined by risk in the RIFLE criteria[51] for (a) all patients ($n=750$), (b) patients with eGFR < 60 mL/min/1.73 m^2 on the index treatment day ($n=160$) and (c) patients with eGFR > 60 mL/min/1.73 m^2 on the index treatment day ($n=590$). Patients in Kaplan–Meier plots were censored on AKI day or last day of treatment, whichever came first.

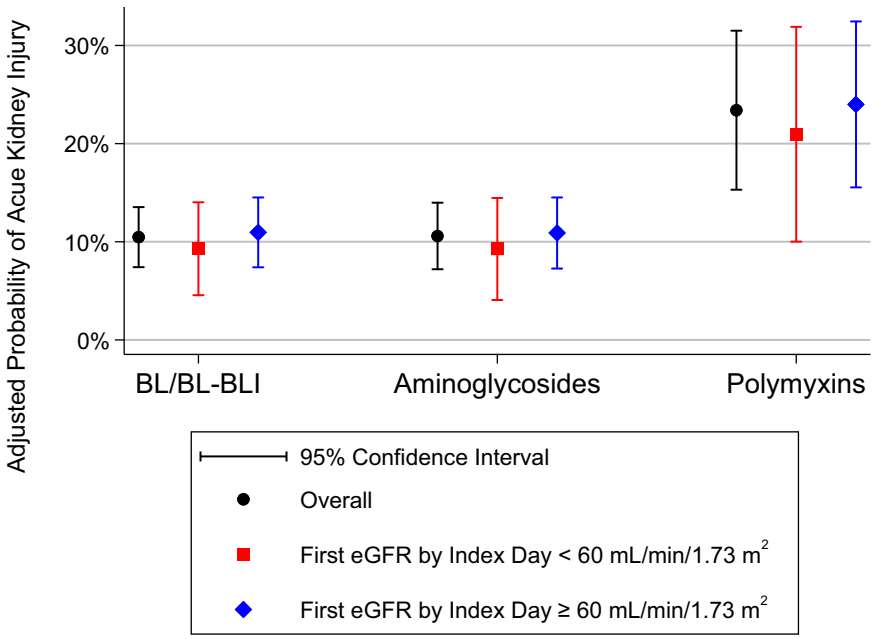

Figure 2. Adjusted probability of treatment-associated AKI defined by risk in the RIFLE criteria[51] stratified by eGFR value on the index treatment day.

(23.4%) had eGFR ≤ 60 mL/min/1.73 m^2, the average age of PB patients was 56.6 years, and fewer than half of patients in the PB group were in the ICU on the index CR-GNI culture day. In contrast, most other studies that evaluated the association between PB treatment and AKI included older, more acutely ill patients with worse baseline renal function.[36,39–41,43–46,58–63] Patients received, on average, 7 days of PB-based therapy in this study, and data indicate that PB-associated AKI increases as a function of treatment duration.[62,63] Finally, the observed associations between PB and AKI relative to non-PB-based therapies on the relative scale were nearly identical between this study (RR: 2.16; 95% CI: 1.31–3.55; OR: 2.71; 95% CI: 1.36–5.40) and a recent large-scale meta-analysis (OR: 2.23; 95% CI: 1.58–3.15).[41] This finding further suggests that baseline and treatment duration differences likely accounted for the lower PB AKI incidence observed in this study relative to others.[64]

Another notable finding in this study was the comparable AKI incidences between patients who received a newer BL/BL-BLI- or AG-containing regimen. AG-associated AKI in this study was found to be 6%–25% lower than that observed in other recent studies that assessed the association between AG treatment and AKI among patients with CR-GNIs.[39,58,65] In the pathogen-specific Combating Antibiotic-Resistant Enterobacteriaceae (CARE) trial, 16.7% of patients who received plazomicin had AKI, defined as a ≥0.5 mg/dL increase in S_{CR}.[58] Similarly, Pogue *et al.*[39] reported that 23% of patients who received an AG-containing regimen for their drug-resistant *P. aeruginosa* infection experienced AKI, defined by RIFLE criteria, relative to 6% of those who received ceftolozane/tazobactam. It is likely similar factors (e.g. younger population, low proportion of patients with baseline eGFR < 60 mL/min/1.73 m^2 or residence in ICU on the index CR-GNI culture collection date) that accounted for the lower observed PB-associated AKI incidence in this study also contributed to the lower AG-associated AKI incidence proportion. The median duration of AG use in this study was 5 days and available clinical data indicate >5–7 days of AG therapy are needed to cause AKI.[66–68] As shown in Figure 1, there was an accelerated increase in AKI among patients receiving AG for >7 days relative to those receiving a newer BL/BL-BLI-containing regimen.

Although β-lactams can cause AKI,[69] we anticipate the adjusted AKI incidence of 11.9% (95% CI: 8.1%–15.7%) in the newer BL/BL-BLI group was most likely due to their underlying risk factors for AKI[16–21] versus a true drug-associated adverse event.[70,71] Notably, the median treatment duration in the newer β-lactam group was 8 days and most AKI events occurred after 10 days of therapy (Figure S1). This finding suggests the observed AKI incidence in the newer BL/BL-BLI group was more likely related to their underlying disease severity and comorbidities that augmented their risk of experiencing an AKI over time.[70,71] Furthermore, nearly all (92%) patients in the BL/BL-BLI group received other potentially nephrotoxic medications (Table 1) and we speculate this contributed to the observed adjusted AKI incidence in the BL/BL-BLI group. Of note, the factors that likely contributed to the observed AKI cumulative incidence in the BL/BL-BLI group were also responsible, in part, for the observed AKI incidences in the PB and AG groups.[16–21] As such, the proportion of the observed treatment-associated AKI that was actually attributable to either BL/BL-BLI, AG or PB (i.e. attributable AKI risk percentage) in this study was likely less than the observed AKI incidence.

The findings from the AKI–outcomes analyses have important implications for antimicrobial stewardship. Although stewardship encompasses a range of coordinated activities to promote the prudent use of antimicrobials, one of its most critical functions is to ensure patients with serious infections receive effective therapies, in a timely fashion, that maximize clinical response with minimal adverse events.[72,73] Consistent with other studies,[35,40,43–46,74,75] we observed that patients with CR-GNIs

Table 3. Unadjusted and Inverse probability of weighting (IPW)-adjusted comparisons of clinical and healthcare resource utilization outcomes between patients who experienced treatment-associated AKI defined by risk in the RIFLE criteria[51] relative to patients who did not experience treatment-associated AKI

	Unadjusted comparisons			IPW-adjusted comparisons		
	No treatment-associated AKI ($n=659$)	Treatment-associated AKI ($n=91$)	*P* value	No treatment-associated AKI ($n=659$)	Treatment-associated AKI ($n=91$)	*P* value
30 Day mortality, % (95% CI)	4.4 (3.0–6.3)	17.6 (10.4–27.0)	<0.001	4.5 (2.9–6.1)	16.7 (9.4–24.1)	0.001
In-hospital mortality, % (95% CI)	5.3 (3.7–7.3)	20.9 (13.1–30.7)	<0.001	5.6 (3.8–7.3)	18.5 (10.8–26.2)	0.001
In-hospital mortality or discharge to hospice, % (95% CI)	11.2 (8.9–13.9)	30.8 (21.5–41.3)	<0.001	11.7 (9.3–14.2)	26.7 (17.9–35.4)	0.001
Discharge destination among all patients: home versus other, % (95% CI)	32.9 (29.3–36.7)	26.4 (17.7–36.7)	0.209	32.0 (28.5–35.5)	29.5 (18.9–40.0)	0.651
Mean hospital LOS (days) from index treatment day to hospital discharge, % (95% CI)[a]	14.3 (13.1–15.5)	25.8 (11.4–40.3)	<0.001	14.8 (13.4–16.2)	18.5 (15.2–21.8)	0.032
Mean hospital costs from index treatment day to hospital discharge (95% CI)[a]	$37 027 ($32 531–$41 523)	$68 046 ($37 154–$98 937)	<0.001	$38 763 ($33 959–$43 566)	$49 192 ($39 697–$58 686)	0.043
30 Day readmission among survivors, % (95% CI)	24.7 (21.3–28.3)	26.4 (16.7–38.1)	0.751	24.7 (21.3–28.0)	29.8 (18.4–41.2)	0.396

Baseline covariates included as predictor variables included US census region, number of hospital beds, type of hospital (teaching versus non-teaching), age, sex, race (white versus other), admission source (home/community versus other), history of hospitalization in the 6 months prior to index culture, baseline eGFR category, eGFR on index treatment day, CCI score, hospital LOS prior to the index CR-GN culture, residence in ICU on the day of the index CR-GN culture, receipt of MV on the day of the index CR-GN culture, CR-GN pathogen on the day of index culture (*P. aeruginosa* versus *Klebsiella* sp. versus other), infection type (HABP/VABP versus cUTI versus BSI), the treatment groups (newer BL/BL-BLI, AG or PB), antibiotics received between admission and index treatment day (aminoglycoside versus β-lactam versus vancomycin versus other) and receipt of other treatment allocation agents (newer BL/BL-BLI, AG or PB) from index β-lactam, aminoglycoside or polymyxin treatment through to 3 days after β-lactam, aminoglycoside or polymyxin discontinuation.

[a]Index treatment day was first day of treatment with a newer BL/BL-BLI-, AG- or PB-containing regimen.

who experience AKI have a 2- to 3-fold increase in mortality, 4–5 day longer hospital stay and additional hospital costs in excess of $11 000 USD. From a clinical perspective, it is important to recognize that S_{CR} is a crude biomarker that only increases after a substantial amount of kidney injury has already occurred.[76] Because of renal reserve, it is estimated that patients may lose up to 50% of nephrons before S_{CR} increases and AKI cannot be averted by close S_{CR} monitoring.[76,77] Therefore, clinicians and antimicrobial stewards should minimize the use of agents associated with an increased risk of AKI whenever possible as a measure to optimize patient-centric outcomes. From a clinical pathway/formulary perspective, antibiotics that augment the risk of AKI should be designated as non-preferred or second-line agents in patients with CR-GNIs and their use should only be considered in clinical situations when the benefits outweigh the risks (e.g. patient failed a first-line agent that has a lower potential to cause AKI).

Several limitations should be noted when interpreting the findings of this study. First are those inherent to this study design, which include study selection bias, unmeasured confounding, and confounding by indication. Study design restrictions, stratified analyses and multivariable methods (IPW, multivariable regression modelling) were used to minimize the influence of the potential systematic biases.[78] For example, our study design produced treatment groups that were largely comparable at baseline. Infection type and concurrent treatment with a tetracycline-like antibiotic were

the only baseline variables that were significantly different between treatment groups [i.e. hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia (HABP/VABP) and concurrent tetracycline use were more pronounced in PB patients) and significantly associated with AKI. The persistence of findings in the multivariable analyses after accounting for these and other baseline variables suggests confounding likely had a minimal impact on the observed exposure–outcome findings. However, these methods cannot account for unmeasured confounders between groups and some degree of caution should be exercised when interpreting the results.

Data on antibiotic dosing and drug concentrations were not available in the PHD. As such, we were unable to assess the potential impact of drug exposure or dosing regimens received on the observed treatment-associated AKI cumulative proportions. Patients with infections due to carbapenem-resistant *A. baumannii* or *S. maltophilia* were excluded since most of the newer agents apart from cefiderocol have reliable *in vitro* activity against these CR-GNs. As such, it is unknown how applicable these findings are to other populations that were not included in the study. Third, we were unable to assess the effect of time to receipt of a microbiologically active agent because susceptibility data were not available in many patients and the impact of delayed appropriate therapy on the observed outcomes could not be determined as part of this study. Fourth, potential misclassification may be present from using diagnosis codes, microbiological culture and treatment data to define patients with HABP/VABP and cUTI due to CR-GNI. In addition, some HABP/VABP cases may have been missed as pneumonia and are often undercoded in hospitalized ICU patients.[79–81] Since there are no specific codes for cUTI, a composite case definition was utilized based on a previous study.[82,83] However, the codes used to define the study cohort have been previously validated to have high positive predictive values.[84–88]

In conclusion, there are two critical components of optimal antimicrobial chemotherapy. First, therapy should be *efficacious*; second, therapy should be *non-toxic*. A potentially serious adverse effect associated with some of the agents used for patients with CR-GNIs, namely the PB, is AKI.[36–46] Although caution should be exercised when interpreting the findings due to the observational nature of the study, we observed that patients who received PB had a significantly higher incidence of AKI. Furthermore, patients with CR-GNIs who experienced treatment-associated AKI defined by the RIFLE criteria had substantial increases in morbidity, mortality and healthcare resource utilization, with each AKI event resulting in excess hospital costs of ≥11 000 USD. As data indicate AKI cannot be averted by close S_{CR} monitoring,[76,77] clinicians should minimize use of agents associated with an increased risk of AKI whenever possible.

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Author contributions

T.P.L. and B.H.N. led the development of the research question, study design, implementation of the study protocol, analysis and interpretation of data, and drafting the report, along with E.Y.., E.N.O. and A.H.W. All authors provided critical reviews and final approval of the manuscript.

Supplementary data

Figure S1, Tables S1 to S4 and Appendices A to E are available as Supplementary data at *JAC* Online.

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