J Antimicrob Chemother
doi:10.1093/jac/dkz457

Journal of Antimicrobial Chemotherapy

Aminoglycoside versus carbapenem or piperacillin/tazobactam treatment for bloodstream infections of urinary source caused by Gram-negative ESBL-producing Enterobacteriaceae

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Received 30 June 2019; returned 19 August 2019; revised 14 September 2019; accepted 4 October 2019

Objectives: We studied the performance of aminoglycosides in treating bloodstream infections (BSIs) of urinary source caused by ESBL-producing Enterobacteriaceae (ESBL-EB).

Methods: In a retrospective study of 193 patients with a clinical diagnosis of urinary tract infection, pyelonephritis or urosepsis and blood and urine cultures positive for ESBL-EB, patients were grouped according to whether they were treated with an aminoglycoside, a carbapenem or piperacillin/tazobactam. Multivariate analysis was used to define risk factors for mortality with inverse probability of treatment weighting used to minimize confounding. The primary efficacy outcome was 30 day mortality. The primary safety outcome was acute kidney injury (AKI) at 14 days.

Results: Mean age was 79.3 years. Dementia, chronic kidney disease and the presence of a urinary catheter were common. Thirty-two (16.6%) patients died and risk factors for mortality included age, high Charlson score, presentation with severe sepsis/septic shock and infection with bacteria other than *Escherichia coli*. Aminoglycosides were non-inferior compared with other antibiotics regarding 30 day mortality [13.0% versus 21.2%, respectively; adjusted risk difference=10.29% (−0.82% to 21.41%)], but did not reach non-inferiority for bacteriuria recurrence [48.9% versus 44.7%, respectively; adjusted risk difference=−8.72% (−30.87% to 13.43%)]. AKI developed at a similar rate in both treatment groups: 12.0% versus 10.6%, respectively [OR=1.14 (0.46–2.81)]. Aminoglycosides were more efficacious in *E. coli* infections compared with other ESBL-EB.

Conclusions: We demonstrated the efficacy and safety of aminoglycosides in treating BSI of urinary source caused by ESBL-EB. This carbapenem-sparing approach can assist in avoiding excessive carbapenem use without compromising outcomes.

Introduction

Infections with ESBL-producing Enterobacteriaceae (ESBL-EB) are a significant problem clinically and epidemiologically.[1] There is an ongoing debate considering the ideal antibiotic treatment in ESBL-EB bloodstream infections (BSIs). Carbapenems are considered the treatment of choice, but some publications have also demonstrated good results with β-lactam/β-lactamase inhibitor combinations and specifically piperacillin/tazobactam.[2–8] There is little and conflicting evidence regarding other antibiotics.[6,9,10] Recent studies showed the efficacy of carbapenem-sparing treatments as empirical therapy.[4,11] However, Harris *et al.*[7] failed to demonstrate non-inferiority for piperacillin/tazobactam against ESBL BSI in the only randomized controlled trial performed. It has been suggested that the efficacy of a specific antibiotic depends on the bacteria causing the infection, the ESBL enzyme causing antibiotic resistance, the inoculum and the site of infection; this may explain some of the conflicting results in different studies.

Urinary tract infections (UTIs) are commonly caused by Enterobacteriaceae. These infections may be complicated by BSI.[12–15]

Aminoglycosides are active against Gram-negative aerobic bacteria including resistant Enterobacteriaceae. Aminoglycoside concentration in the urine is high, which assists rapid source control. Several guidelines recommend aminoglycosides as monotherapy for UTI.[16,17] In the last decade, the enthusiasm to prescribe aminoglycosides has diminished because of concerns related to renal toxicity, which occurs in 5%–24% of patients.[16–18] Risk factors for nephrotoxicity include prolonged treatment,

multiday dosing, gentamicin (compared with amikacin), chronic kidney disease, older age, shock and simultaneous nephrotoxic agents.[18–21] A meta-analysis comparing aminoglycoside monotherapy with other drugs showed similar efficacy in clinical cure, but inferiority in microbiological cure.[22] Despite these concerns, the emergence of resistant bacteria necessitates a reconsideration of the advantages as well as concerns regarding aminoglycosides.

Since aminoglycosides are active against ESBL-EB, and are used as monotherapy in UTI, we conducted a retrospective cohort study to evaluate the efficacy and safety of aminoglycoside monotherapy as definitive treatment in ESBL-EB BSI of urinary origin.

Methods

Setting and participants

We included adult patients admitted to the Wolfson Medical Center between 1 January 2014 and 31 December 2017, who had a positive blood culture for ESBL-EB and a positive urine culture with the same bacteria, as well as a clinical diagnosis of UTI or pyelonephritis or urosepsis, and were treated with an aminoglycoside, carbapenem or piperacillin/tazobactam after receiving culture results (definitive therapy).

We searched the microbiology database for all ESBL-EB-positive blood cultures. ESBL positivity for blood cultures was tested using the disc method. For each patient, we searched for a positive urine culture with the same bacteria taken within # 5 to ! 5 days of the blood culture. We included all patients for which the source of the infection was the urinary system and that were treated with an aminoglycoside, a carbapenem or piperacillin/tazobactam for more than 48 h. Exclusion criteria were other sources of bacteraemia and resistance to the antibiotic given. We also excluded patients with polymicrobial bacteraemia and patients who did not complete 48 h of appropriate treatment due to death or other reasons.

Patients were grouped according to the treatment they received: aminoglycoside versus carbapenem or piperacillin/tazobactam in an ITT manner.

Data collection

Patient charts were summarized in a tabular manner regarding past and present medical history and treatment. The Charlson comorbidity score was calculated.[23] Severe sepsis and septic shock were defined as sepsis with at least one organ dysfunction or tissue hypoperfusion, and sepsis with hypoperfusion not responsive to fluid resuscitation, in accordance with the Surviving Sepsis Campaign definitions.[24] Patient kidney function was recorded at baseline and at the end of treatment. Estimated glomerular filtration rate (GFR) was calculated using the CockcroftÐGault equation. Urine cultures were followed up to 90 days to assess recurrence of bacteriuria.

Outcomes

The primary efficacy outcome was death from any cause at Day 30 after presentation with ESBL-EB BSI. Secondary efficacy outcomes were a combined outcome of death at 30 days or therapy switch (excluding a switch to oral treatment) or recurrence of bacteriuria with the same bacteria in 90 days. The primary safety outcome was acute kidney injury (AKI) at 14 days after presentation defined according to Kidney Disease Improving Global Outcomes (KDIGO) guidelines[25] as a rise of 50% or more than 0.3 mg/dL from baseline creatinine. The secondary safety outcome was AKI at 14 days or treatment switch due to safety problems or concerns.

Statistical analysis

Statistical analysis was performed with SAS 9.4. Groups were compared using a v^2 test for categorical variables and StudentÕst-test for continuous variables. We assessed risk factors for 30 day mortality using logistic regression. Variables significantly associated with mortality in a univariate analysis ($P<0.1$) were entered into the logistic regression analysis using backward elimination. Results are presented as OR and 95% CI (and P value).

To compare efficacy of the treatment groups, we created a propensity-score weighted sample (keeping all subjects in the sample), using the inverse probability of treatment weighting (IPTW) method, where the weights were stabilized by weighting the two groups against the full sample. Variables included in the model were age, sex, baseline GFR, immunocompromised state, dementia, Charlson comorbidity score, nosocomial infection, severe sepsis or septic shock at presentation and time to appropriate treatment. After weighting of the treatment groups using the IPTW score, we assessed efficacy using a risk difference calculation for non-inferiority; the margin was set at 10%.

To assess aminoglycoside effects in patients who presented without severe sepsis or septic shock we created another IPTW not including the presentation variable (severe sepsis, septic shock or none).

Ethics

The study was approved by the hospitalÕs Ethics Committee (approval number 0188-17-WOMC). There was no informed consent in this retrospective study.

Results

Participants

Of 889 ESBL-EB BSIs screened, 218 BSIs were included in the final analysis (Figure 1). Of these, in 193 BSIs the first definitive treatment was with an aminoglycoside (108 cases), a carbapenem (73 cases) or piperacillin/tazobactam (12 cases). The patients treated with an aminoglycoside received amikacin as first definitive treatment in 74 cases and gentamicin in 34 cases. All of them were treated in a once-daily dosing strategy. Patients treated with a carbapenem received ertapenem in all but one case who received meropenem.

Average age was 79.3 years. Dementia, chronic kidney disease and presence of urinary hardware (mostly chronically indwelling catheters) were common. Known risk factors for ESBL-EB, including ESBL infection or colonization, previous hospitalizations and antimicrobial treatment, were common. Only a small percentage were immunocompromised. Aminoglycoside-treated patients were less independent and had better baseline GFR and lower Charlson comorbidity scores, but higher rates of dementia (Table 1).

The most common bacteria were *E. coli* (followed by *Klebsiella* spp.). Infection was nosocomial in 22.3% of cases; most patients were admitted to internal medicine departments. Thirty percent presented with severe sepsis or septic shock, but only 3.1% were admitted to the ICU. Septic shock and severe sepsis were less common in patients treated with an aminoglycoside and none of them was admitted to the ICU (Table 1).

The median length of appropriate antibiotic treatment (including post-discharge therapy) was 8 days (IQR=7Ð10 days) and the median length of treatment with an aminoglycoside was 7 days (IQR=6Ð9 days).

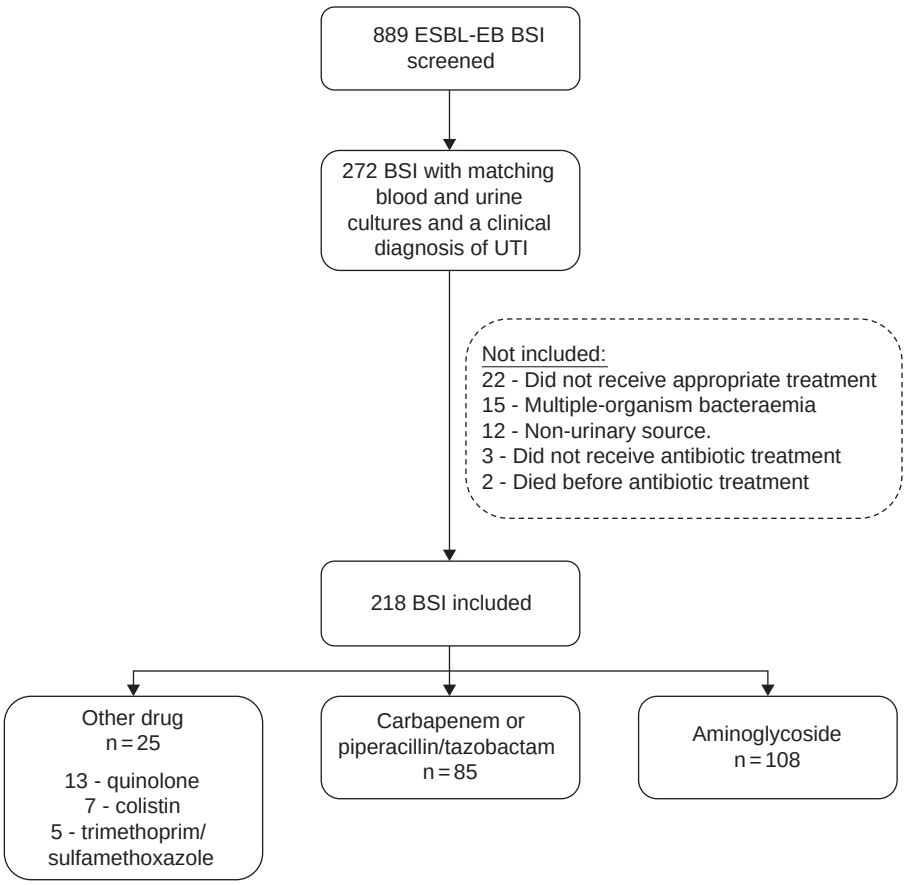

Figure 1. Patients included in the study and grouping according to the Þrst antibiotic treatment administered (ITT).

Aminoglycoside efÞcacy

The 30 day mortality rate was 13.0% (14/108 patients) among patients who received deÞnitive therapy with an aminoglycoside and 21.2% (18/85 patients) among patients treated with a carbapenem or piperacillin/tazobactam. In multivariate analysis, risk factors for mortality were age, Charlson comorbidity index, presentation with severe sepsis or septic shock and type of bacteria. In the unadjusted population, appropriate empirical antibiotic treatment and type of deÞnitive antibiotic treatment were not signiÞcantly associated with mortality (Table 2).

E. coliwas associated with the lowest risk for mortality (15/127 patients; 11.8%), Klebsiellaspp. with moderate risk (12/61 patients; 19.7%) and other Enterobacteriaceae with a higher risk for mortality (10/30 patients; 33.3%), regardless of the antibiotic given. The mean times to appropriate therapy were 1.85, 1.74 and 1.33 days from presentation, respectively.

After IPTW adjustment, an aminoglycoside remained non-inferior to a carbapenem or piperacillin/tazobactam (Table 3).

Treatment was switched in 15.7% (17 cases) of patients in the aminoglycoside group versus 7.1% (6 cases) of patients in the carbapenem or piperacillin/tazobactam group. Change to oral therapy in both groups was not considered as a switch. Reasons for treatment switch were: lack of response to therapy in 4.6% (5 cases) versus 2.4% (2 cases), respectively; toxicity or fear of toxicity in 7.4% (8 cases) versus 0%, respectively; and acquisition of an additional infection necessitating use of different antibiotics in 3.7% (4 cases) versus 4.7% (4 cases), respectively.

We also assessed recurrence of bacteriuria (symptomatic or asymptomatic) within 90 days. Recurrences were not signiÞcantly higher in the aminoglycoside group (48.9% versus 44.7%) [OR=1.43 (95% CI=0.58Ð3.54)], but did not reach non-inferiority [adjusted risk difference # 8.72% (# 30.87% to 13.43%)], although the study was not powered to show a statistically signiÞcant difference.

Aminoglycoside safety

AKI developed at a similar rate in both treatment groups; 12.0% (13 cases) in the aminoglycoside group and 10.6% (9 cases) in the carbapenem or piperacillin/tazobactam group [OR=1.14 (95% CI=0.46Ð2.81)]. We assumed that treatment switch might have prevented some AKI events, so we assessed a combined outcome of AKI or treatment switch due to toxicity or safety concerns. Since there were no cases of treatment switch due to safety concerns in the carbapenem or piperacillin/tazobactam group, the combined safety outcome occurred nearly twice as much in the aminoglycoside group, yet this was not statistically signiÞcant [18.5% (20 cases) in the aminoglycoside group and 10.6% (9 cases) in the carbapenem or piperacillin/tazobactam group; OR=1.89 (95% CI=0.81Ð4.41)].

Table 1. Baseline characteristics of patients

	Total (*N*=193)	Aminoglycoside (*N*=108)	Carbapenem or piperacillin/tazobactam (*N*=85)	*P*
Age (years), mean (SD)	79.3 (11.0)	79.7 (10.8)	78.8 (11.3)	0.573
Male	102 (52.9)	55 (50.9)	47 (55.3)	0.564
Dwelling				0.535
home	132 (68.4)	76 (70.4)	56 (65.9)	
long-term care facility	61 (31.6)	32 (29.6)	29 (34.1)	
Function				0.020
independent	67 (34.7)	30 (27.8)	37 (43.5)	
partially dependent	27 (14.0)	13 (12.0)	14 (16.5)	
dependent	99 (51.3)	65 (60.2)	34 (40.0)	
Immunocompromised	11 (5.7)	4 (3.7)	7 (8.2)	0.218
Renal function				
GFR (mL/min), mean (SD)	66.8 (26.0)	74.8 (21.3)	56.7 (28.0)	<0.001
GFR >60 mL/min	120 (62.2)	84 (77.8)	36 (42.4)	
GFR >30 to ≤60 mL/min	57 (29.5)	22 (20.4)	35 (41.2)	
GFR >15 to ≤30 mL/min	11 (5.7)	1 (0.9)	10 (11.8)	
GFR ≤15 mL/min	5 (2.6)	1 (0.9)	4 (4.7)	
dialysis	2 (1.0)	1 (0.9)	1 (1.2)	
Foreign body	32 (16.6)	12 (11.1)	20 (23.5)	0.031
Vascular catheter	3 (1.6)	2 (1.9)	1 (1.2)	1.000
Urinary hardware	60 (31.1)	29 (26.9)	31 (36.5)	0.162
urinary catheter	52 (26.9)	28 (25.9)	24 (28.2)	
nephrostomy	5 (2.6)	1 (0.9)	4 (4.7)	
Urinary tract malignancy	9 (4.7)	3 (2.8)	6 (7.1)	0.186
Urinary tract surgery (6 months)	17 (8.8)	4 (3.7)	13 (15.3)	0.009
Nephrolithiasis	31 (16.1)	14 (13.0)	17 (20.0)	0.236
Diabetes	72 (37.3)	41 (38.0)	31 (36.5)	0.881
Congestive heart failure	29 (15.0)	12 (11.1)	17 (20.0)	0.105
Cerebrovascular disease	55 (28.5)	34 (31.5)	21 (24.7)	0.337
COPD	30 (15.5)	15 (13.9)	15 (17.7)	0.550
Malignancy	23 (11.9)	10 (9.3)	13 (15.3)	0.263
Dementia	70 (36.3)	50 (46.3)	20 (23.5)	<0.001
Charlson comorbidity index, mean (SD)	3.2 (2.3)	2.7 (1.9)	3.8 (2.4)	<0.001
Infection/colonization with ESBL-EB in the last 6 months	68 (35.2)	39 (36.1)	29 (34.1)	0.879
Infection/colonization with another MDR bacteria in the last 6 months	17 (8.8)	5 (4.6)	12 (14.1)	0.038
Clostridioides difficile infection in the last 6 months	5 (2.6)	1 (0.9)	4 (4.7)	0.171
Antibiotic treatment in the last 6 months	123 (63.7)	66 (61.1)	57 (67.1)	0.452
cephalosporins	86 (44.6)	49 (45.4)	37 (43.5)	0.884
BLBLI	32 (16.6)	16 (14.8)	16 (18.8)	0.559
aminoglycosides	24 (12.4)	18 (16.7)	6 (7.1)	0.050
carbapenems	15 (7.8)	4 (3.7)	11 (12.9)	0.028
quinolones	33 (17.1)	21 (19.4)	12 (14.1)	0.344
Hospitalization in the last 6 months	126 (65.3)	63 (58.3)	63 (74.1)	0.023
Hospitalization days in the last 6 months, mean (SD) [range]	16.7 (14.2) [2–84]	15.0 (11.2) [2–63]	18.5 (16.7) [2–84]	0.188
Nosocomial infection	43 (22.3)	22 (20.4)	21 (24.7)	0.491
Days between admission and presentation, mean (SD)	24.8 (22.8)	28.6 (24.8)	20.8 (20.3)	
Bacteria				0.010
E. coli	118 (61.1)	76 (70.4)	42 (49.4)	
Klebsiella spp.	50 (25.9)	20 (18.5)	30 (35.3)	
other Enterobacteriaceae	25 (13.0)	12 (11.1)	13 (15.3)	
Department				0.171
internal medicine	171 (88.6)	99 (91.7)	72 (84.7)	
urology	16 (8.3)	8 (7.4)	8 (9.4)	

Continued

Table 1. Continued

	Total (N=193)	Aminoglycoside (N=108)	Carbapenem or piperacillin/ tazobactam (N=85)	P
other surgical departments	6 (3.1)	1 (0.9)	5 (5.9)	
ICU admission	6 (3.1)	0 (0.0)	6 (7.1)	0.007
Presentation				<0.001
severe sepsis	38 (19.7)	16 (14.8)	22 (25.9)	
septic shock	20 (10.4)	5 (4.6)	15 (17.7)	
Days until appropriate treatment, mean (SD)	1.7 (1.8)	1.7 (1.9)	1.7 (1.7)	0.896
Source control[a]	16 (8.3)	3 (2.8)	13 (15.3)	0.007

BLBLI,b-lactam/ b-lactamase inhibitor.
Patient characteristics according to the Þrst deÞnitive antibiotic treatment.
Results are presented asn (%), unless otherwise stated.
[a]An invasive procedure (excluding catheter insertion) was needed and performed.

Table 2. Multivariate analysis of risk factors for mortality

		Multivariate analysis		
Variable	Univariate analysis, P	OR	95% CI	P
Age	0.065	1.04	0.99Ð1.09	0.093
Charlson comorbidity index	0.023	1.21	1.01Ð1.46	0.040
Bacteria[a]	0.017	1.78	1.06Ð3.01	0.031
Presentation[b]	0.002	3.85	1.69Ð8.77	0.001
Functional status[c]	0.076			
Appropriate empirical therapy	0.122			
Type of deÞnitive therapy[d]	0.128			
Length of appropriate therapy (days)	0.726			

Multivariate analysis of the risk factors for mortality using backward elimination logistic regression.
[a]Bacteria: E. coli, Klebsiellaspp.; and other Enterobacteriaceae.
[b]Presentation with severe sepsis or septic shock.
[c]Functional status: independent; partially dependent; and dependent.
[d]An aminoglycoside versus a carbapenem or piperacillin/tazobactam.

Analysis for patients who presented without severe sepsis or septic shock

To avoid selection bias, we analysed a subgroup of patients who presented without severe sepsis or septic shock. For this, we created another IPTW model not including the presentation variable (severe sepsis, septic shock or none). We demonstrated non-inferiority of an aminoglycoside in this subgroup of patients for mortality, mortality and treatment switch, and AKI at 14 days (Table 4).

Relationship between type of bacteria and aminoglycoside efÞcacy

Since we showed a relationship between type of bacteria and mortality, we assessed the relationship between type of bacteria and aminoglycoside efÞcacy. In a subgroup analysis, there was a signiÞcant interaction between type of bacteria and aminoglycoside efÞcacy, showing better outcomes for an aminoglycoside in E. coli BSI (Figure 2).

Discussion

Aminoglycoside efÞcacy

In this study, we showed non-inferiority of an aminoglycoside to a carbapenem or piperacillin/tazobactam for mortality. Since the statistical analysis was performed according to the Þrst deÞnitive treatment, we also assessed a combined outcome of mortality and treatment switch for which we also showed non-inferiority for an aminoglycoside. To our knowledge, this is one of the Þrst studies showing efÞcacy of an aminoglycoside as a single deÞnitive treatment in patients with BSI caused by resistant bacteria.

Treatment of ESBL-EB BSI is a challenge discussed thoroughly in the literature. Although the best clinical experience is with carbapenems, there is an ecological interest in avoiding excessive use of medications from this class. A recent paper [11] looked at empirical therapy of ESBL-EB BSI with carbapenems versus carbapenem-sparing therapy and showed similar efÞcacy, with aminoglycosides speciÞcally having similar efÞcacy to carbapenems.

Table 3. EfÞcacy and safety outcomes

Outcome	Aminoglycoside (N=108), n (%)	Carbapenem or piperacillin/ tazobactam (N=85), n (%)	Non-adjusted OR (95% CI)	Non-adjusted risk difference, % (95% CI)	Adjusted[a] OR (95% CI)	Adjusted[a] risk difference, % (95% CI)
30 day mortality	14 (13.0)	18 (21.2)	0.55 (0.26Ð1.19)	8.21 (# 2.54 to 18.96)	0.51 (0.24Ð1.06)	10.29 (# 0.82 to 21.41)
30 day mortality or treatment switch	26 (24.1)	22 (25.9)	0.91 (0.47Ð1.75)	1.81 (# 10.51 to 14.13)	0.69 (0.36Ð1.31)	7.31 (# 5.26 to 19.87)
Recurrence of bacteriuria within 90 days[b]	22 (48.9)	17 (44.7)	1.18 (0.50Ð2.81)	# 4.15 (# 25.67 to 17.37)	1.43 (0.58Ð3.54)	# 8.72 (# 30.87 to 13.43)
AKI 14 days after starting treatment	13 (12.0)	9 (10.6)	1.14 (0.46Ð2.81)	# 1.32 (# 10.35 to 7.70)		
AKI 14 days after starting treatment or treatment switch due to toxicity or toxicity concern	20 (18.5)	9 (10.6)	1.89 (0.81Ð4.41)	# 7.80 (# 17.67 to 2.07)		

Primary and secondary outcomes for efÞcacy and safety, comparing aminoglycoside with carbapenem or piperacillin/tazobactam. The primary efÞcacy outcome was 30 day mortality and the primary safety outcome was development of AKI 14 days after starting antibiotic treatment.
[a]Adjustment using IPTW. Variables included in the adjustment model: age, sex, baseline GFR, immunocompromised state, dementia, Charlson comorbidity index, nosocomial infection, severe sepsis or septic shock at presentation and time to appropriate treatment. Adjustment was performe d only for efÞcacy outcomes.
[b]In patients who had a follow-up urine culture, N=83.

Table 4. EfÞcacy and safety outcomes in patients without severe sepsis or septic shock

Outcome	Aminoglycoside (N=87), n (%)	Carbapenem or piperacillin/ tazobactam (N=48), n (%)	Non-adjusted OR (95% CI)	Non-adjusted risk difference, % (95% CI)	Adjusted[a] OR (95% CI)	Adjusted[a] risk difference, % (95% CI)
30 day mortality	9 (10.3)	5 (10.4)	0.99 (0.31Ð3.15)	0.07 (# 10.7 to 10.8)	0.54 (0.18Ð1.57)	6.52 (# 5.06 to 18.11)
30 day mortality or treatment switch	18 (20.7)	6 (12.5)	1.83 (0.67Ð4.97)	# 8.19 (# 20.84 to 4.46)	0.69 (0.29Ð1.63)	6.02 (# 8.00 to 20.04)
Recurrence of bacteriuria within 90 days[b]	18 (51.4)	11 (47.8)	1.16 (0.40Ð3.31)	# 3.60 (# 29.89 to 22.68)	1.89 (0.61Ð5.85)	# 15.81 (# 43.28 to 11.66)
AKI 14 days after starting treatment	10 (11.5)	3 (6.3)	1.95 (0.51Ð7.45)	# 5.24 (# 14.83 to 4.34)		
AKI 14 days after starting treatment or treatment switch due to toxicity or toxicity concern	16 (18.4)	3 (6.3)	3.38 (0.93Ð12.26)	# 12.14 (# 22.78 to # 1.5)		

Primary and secondary outcomes for efÞcacy and safety, comparing aminoglycoside with carbapenem or piperacillin/tazobactam, in a subgroup of patients who presented without severe sepsis or septic shock.
[a]Adjustment using IPTW. Variables included in the adjustment model: age, sex, baseline GFR, immunocompromised state, dementia, Charlson comorbidity score, nosocomial infection and time to appropriate treatment. Adjustment was performed only for efÞcacy outcomes.
[b]In patients who had a follow-up urine culture, N=58.

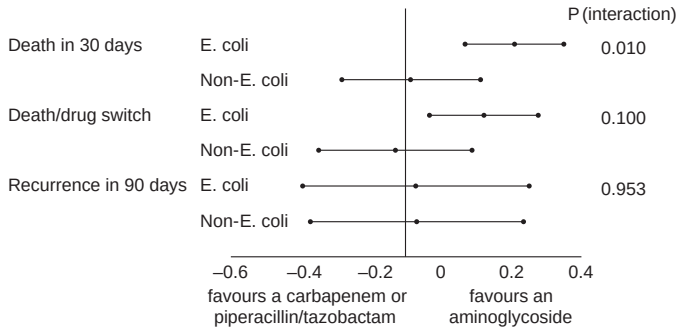

Figure 2. Primary and secondary efÞcacy outcomes comparing an aminoglycoside with a carbapenem or piperacillin/tazobactam, analysed according to type of bacteria (E. coliversus non-E. coli).

When comparing patients treated with an aminoglycoside with those treated with a carbapenem or piperacillin/tazobactam, it is evident that patients treated with an aminoglycoside had less severe disease, with lower rates of severe sepsis or septic shock, no admission to the ICU and a lower burden of chronic illness. This is due to a selection bias, as doctors tend to avoid aminoglycosides in patients with severe disease. This difference between the groups may explain the higher rates of mortality in patients treated with a carbapenem or piperacillin/tazobactam. We included presentation with septic shock in the IPTW, but we believe that adjustment for this bias is partial. Therefore, we also performed a subanalysis including only patients that presented without severe sepsis or septic shock, which showed similar results.

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