Risk factors for acute kidney injury in critically ill patients with bacteraemia by carbapenem non-susceptible Gram negative bacteria

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SUMMARY

The objectives of the present study were to identify risk factors for development of acute kidney injury (AKI) during the treatment of bacteraemia due to carbapenem non-susceptible Gram-negative bacteria (CnS-GNB) and its role on mortality. Data of all patients with bacteraemia by CnS-GNB in the intensive care unit of a tertiary hospital from 2012 to 2016 were included. AKI was defined by AKIN criteria. Secondary outcomes were AKI development in patients treated with colistin and predictors of 14-day mortality. Among 285 episodes of bacteraemia due to CnS-GNB, 84 (29.5%) developed AKI. Multivariate analysis revealed that obesity, septic shock, maximum noradrenaline dose and eGFR<60 mL/min/1.73m^2 upon bacteraemia onset were independently associated with development of AKI. Out of 228 patients receiving colistin, 64 (28.1%) developed AKI. Multivariate analysis found the same factors as before in addition to voriconazole administration. Fourteen-day mortality was 34.2% and was independently associated with bacteraemia by *Pseudomonas aeruginosa*, AKI during bacteraemia treatment, maximum noradrenaline dose, SAPS II and SOFA scores upon bacteraemia onset, whereas appropriate combination therapy and catheter-related bacteraemia were independently associated with better survival. AKI was a frequent complication of bacteraemia by CnS-GNB and was associated with septic shock and baseline renal function impairment. Mortality was higher among patients that developed AKI due to bacteraemia. Colistin should be considered a safe therapeutic option for treating such infections.

Keywords: carbapenem-resistant, acute kidney injury, colistimethate sodium, colistin, carbapenemases, nephrotoxicity.

INTRODUCTION

Carbapenem-resistant Gram-negative bacteria (GNB) are nowadays an important public health issue, since carbapenems were considered until recently one of the most potent antibiotic class for the treatment of nosocomial infections due to their activity against extended spectrum beta-lactamase (ESBL) producers [1, 2]. Carbapenem resistance is more commonly found in Enterobacteriaceae, especially *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* [3, 4]. The worldwide dissemination of carbapenem-resistant GNB has led to increased use of colistin, aminoglycosides, tigecycline, fosfo-

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mycin and the newer category of second-generation beta-lactam/beta-lactamase inhibitor combinations, such as ceftazidime/avibactam [1, 3-5].

Bloodstream infections (BSI) among critically ill patients are associated with high rates of complications, including acute kidney injury (AKI) [6, 7]. The risk for AKI development during the treatment of infections caused by carbapenem-resistant GNB is higher since two of aforementioned therapeutic options, colistin and aminoglycosides, are nephrotoxic [4, 5, 8-16]. Colistin related AKI varies significantly in previous studies from 23.6% to 52.8%, with administration of high dose of colistin being the most prominent risk factor for its development [9, 11, 13-20].

The aim of the present study was to identify risk factors for development of AKI during treatment of BSI due to carbapenem non-susceptible GNB (CnS-GNB) and its role on mortality.

PATIENTS AND METHODS

Study design

This is a retrospective cohort study carried out at the Intensive Care Unit (ICU) of the University General Hospital of Patras, Greece, during a five-year period (2012-16). All adult patients (≥18 years old) with BSI caused by CnS-GNB were identified by the microbiology database. All patients receiving renal replacement therapy upon BSI onset (due to chronic kidney injury or AKI prior to BSI onset) were excluded from the study. Data were obtained by patients' chart reviews and the ICU computerized database (Criticus™, University of Patras, Greece). The study was conducted in accordance with the Declaration of Helsinki and was carried out under the Hospital Surveillance Program for infections by multidrug resistant bacteria of ICU patients and was approved by the Hospital Ethical Committee (No: 434).

Initially, patients who developed AKI were compared to those with no AKI. Then, in a second analysis, patients receiving colistin were included in order to ascertain the factors that may contribute to the nephrotoxicity of colistin. In a third analysis, the role of AKI on mortality was assessed, by investigating potential predictors of 14-day mortality of BSI by CnS-GNB, including patients that were on renal replacement therapy upon BSI onset.

Variables and definitions

Variables assessed were demographic characteristics (age and gender), body mass index (BMI), co-morbidities, reason of ICU admission, severity of illness (as assessed by SAPS II, SOFA scores), estimated glomerular filtration rate (eGFR) upon admission in ICU and BSI onset, site of infection, presence of septic shock, dosage of noradrenaline administration, microorganism(s) isolated, medications administered (antibiotics, antifungals, corticosteroids and nephrotoxic medications). Antibiotic, antifungal and corticosteroid administration were included in our analysis if the patient had received the aforementioned treatment for more than 48h. Nonsteroidal anti-inflammatory drugs, loop diuretics, iodate contrast, renin-angiotensin system blockers, aminoglycosides, glycopeptides, trimethoprim/sulfamethoxazole, voriconazole intravenously, liposomal amphotericin B were considered as nephrotoxic medications. Infection was categorized as sepsis or septic shock according to the definition proposed by the Third International Consensus Definitions for Sepsis and Septic Shock [21]. Serum creatinine measurements were performed daily, and AKI was assessed up to 14 days from the BSI onset or until death before day 14. AKI and classification of its severity (stages 1 to 3) was defined according to the Acute Kidney Injury Network (AKIN), creatinine and urine output criteria [8]. GFR was determined using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [22]. Institutional guidelines

Table 1 - Institutional guidelines concerning the maintenance dose of colistin (colistimethate sodium) according to estimated Glomerular Filtration Rate (eGFR).

eGFR	*Maintenance dose*
>70 ml/min/1.73 m²	4.5 million IU every 12 hours
50-69 ml/min/1.73 m²	3.5 million IU every 12 hours
30-49 ml/min/1.73 m²	2.5 million IU every 12 hours
20-29 ml/min/1.73 m²	2 million IU every 12 hours
<20 ml/min/1.73 m²	1.5 million IU every 12 hours
Intermittent hemodialysis	1 million IU every 12 hours; additional 30% of the daily dose on day of hemodialysis
Continuous renal replacement	9-12 million IU in two or three daily doses

All patients received a loading dose of 9 million IU independently of the renal function

concerning the use of colistin (colistimethate sodium; Colistin/Norma®, Norma Hellas A.E., Athens Greece) recommended the use of a loading dose of 9 million IUs independently of the renal function. Maintenance dose depended of the eGFR and are shown in Table 1. Measurement of vancomycin and aminoglycosides' serum levels was performed in our hospital during the study period, but not for colistin.

Identification and antibiotic susceptibility

Two blood sets from peripheral sites and one from the central venous line, as well as cultures from the suspected site of infection (bronchial secretions, urine, pleural or peritoneal fluid, pus, catheter tip etc.) were obtained and sent to the microbiology laboratory. Gram negative bacteria were identified using the Vitek 2 Advanced Expert System (bioMérieux, Marcy l'Etoile, France) and antibiotic susceptibility was performed by the agar disc diffusion method. Susceptibility to carbapenems (meropenem, imipenem), colistin and tigecycline was determined by the Etest (bioMérieux). The results were interpreted according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines [23].

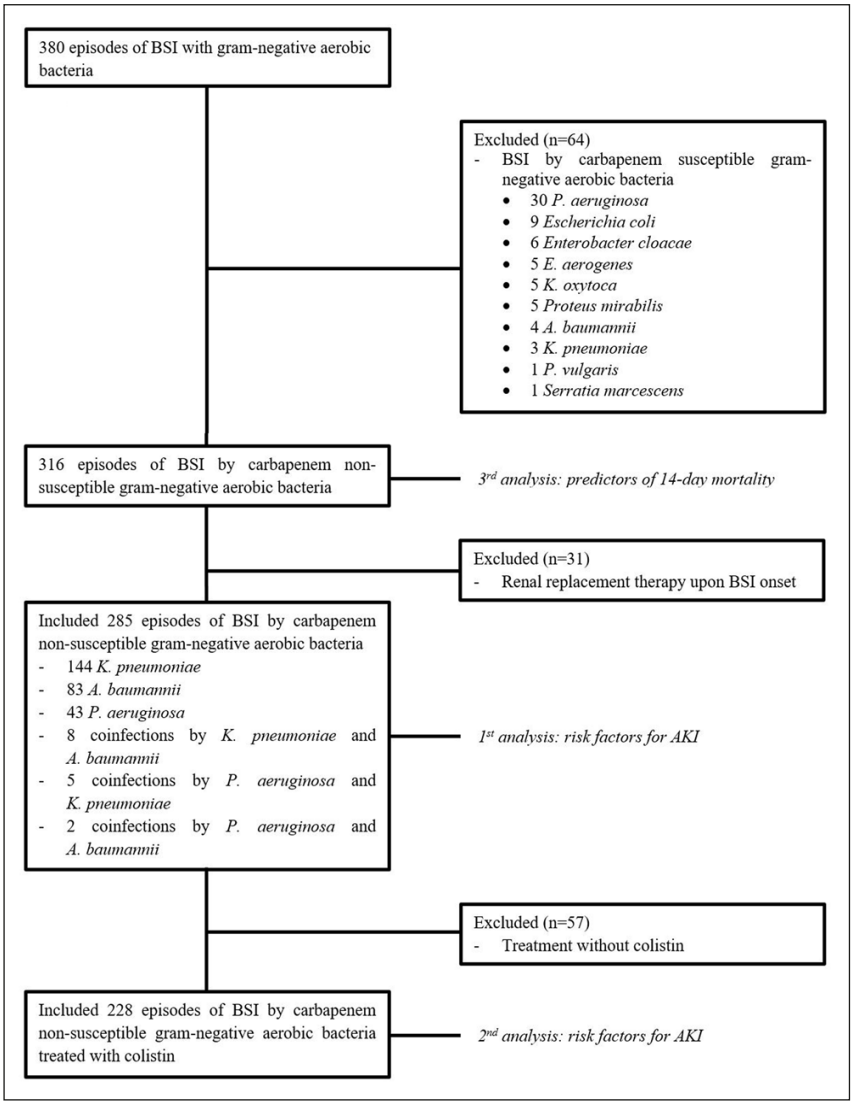

Figure 1 - Flowchart of study patients.

Note:
BSI = bloodstream infections.

Isolates intermediate or resistant to any carbapenem were considered as non-susceptible.

Statistical analysis

SPSS version 23.0 (SPSS, Chicago, IL) was used for data analysis. Categorical variables were analyzed by using the Fisher exact test or chi^2 and continuous variables with Mann-Whitney *U*-test or ANOVA, as appropriate. Backward stepwise multiple logistic regression analysis used all those variables from the univariate analysis with a $P<0.1$. Factors contributing to multicollinearity were excluded from the multivariate analysis. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to evaluate the strength of any association. $P<0.05$ was considered statistically significant.

RESULTS

During the study period, 380 BSI due to Gram-negative aerobic bacteria were observed. Sixty-four were excluded from the study because carbapenem susceptible pathogens were isolated and 31 because the patients were on renal replacement therapy upon BSI infection (Figure 1). A total 285 episodes due to CnS-GNB were included in the final analysis, with the majority being due to *K. pneumoniae* (n=144), followed by *A. baumannii* (n=83), *P. aeruginosa* (n=43), whereas, 15 polymicrobial infections were observed (eight coinfections by *K. pneumoniae* and *A. baumannii*, five coinfections by *P. aeruginosa* and *K. pneumoniae* and two coinfections by *P. aeruginosa* and *A. baumannii*).

A total of 84 out of 285 patients (29.5%) developed AKI (33 AKI 1, 34 AKI 2 and 17 AKI 3; 12 patients received renal replacement therapy due to AKI) during the first 14 days of BSI onset. Results of the univariate analysis of risk factors for AKI development are depicted in Tables 2a and 2b. Multivariate analysis revealed that obesity ($P=0.020$; OR 2.5; 95% CI 1.2-5.3), septic shock ($P=0.023$; OR 3.6; 95% CI 1.2-10.7), maximum noradrenaline dose ($P<0.001$; OR 1.1; 95% CI 1.0-1.1) and eGFR upon BSI onset <60 mL/min/1.73 m^2 ($P<0.001$; OR 4.2; 95% CI 2.0-9.0) were independently associated with development of AKI.

Among the 285 patients, 228 were treated with colistin and were included in the second analysis. Sixty-four (28.1%) among them developed AKI. Results of the univariate analysis of risk factors for AKI among patients treated with colistin are shown in Tables 3a and 3b. Obesity ($P=0.008$; OR 3.2; 95% CI 1.4-7.6), septic shock ($P=0.037$; OR 3.9; 95% CI 1.1-14.3), maximum noradrenaline dose ($P<0.001$; OR 1.1; 95% CI 1.0-1.1), eGFR upon BSI onset <60 mL/min/1.73 m^2 ($P=0.001$; OR 4.6; 95% CI 1.9-11.2) and voriconazole administration ($P=0.048$; OR 6.8; 95% CI 1.0-46.1) were independently associated with AKI.

Fourteen-day mortality was 34.2% (108 out of 316 patients). Results of the univariate analysis of predictors of 14-day mortality are shown in Tables 4a and 4b. Multivariate analysis revealed that mortality was independently associated with BSI by *P. aeruginosa* ($P=0.002$; OR 3.4; 95% CI 1.6-7.2), AKI after BSI onset ($P=0.042$; OR 1.5; 95% CI 1.0-2.1), septic shock ($P<0.001$; OR 3.6; 95% CI 1.8-6.9), SOFA score upon BSI onset ($P=0.004$; OR 1.2; 95% CI 1.1-1.3), SAPS II upon BSI onset ($P=0.002$; OR 1.1; 95% CI 1.0-1.1), whereas appropriate combination therapy ($P=0.015$; OR 0.39; 95% CI 0.18-0.83) and catheter-related BSI (P 0.045; OR 0.47; 95% CI 0.22-0.98) were independently associated with better survival.

DISCUSSION

In the present study 29.5% of bacteraemic patients with CnS-GNB developed AKI during the first 14 days from BSI onset, which was in accordance with previous studies (29.2% to 39.8%) [7, 11, 24]. In the subgroup of patients treated with colistin, AKI rate was 28.1%. There are significant differences in the literature among reported rates of nephrotoxicity during colistin treatment ranging from 23.6% to 50.6% [9, 11, 13, 14, 16-20, 25]. There are many explanations for this variation, including application of different criteria (RIFLE *vs* AKIN), variety of infections, differences in severity of infection (patients hospitalized in general wards *vs* critically ill patients), specific populations (obese) and various colistin's dosing regimens [9-20].

Based on the results of our study, the main factor for the development of AKI is the occurrence of septic shock and its severity, which was indicated by the maximum dose of noradrenaline. Noradrenaline is the vasopressor of choice in septic shock and its role on AKI can be due to multiple reasons like the need of increased dosage when severe and refractory hypotension is present, as

Table 2a - Univariate analysis of risk factors for acute kidney injury (AKI) during the first 14 days of bloodstream infection (BSI) onset due to carbapenem non-susceptible gram-negative bacteria

Characteristics	*No AKI (n=201)*	*AKI (n=84)*	*P*
Demographics			
Age (years)	54.7 ± 18.1	60.9 ± 17.2	0.008
Male gender	144 (71.6%)	59 (70.2%)	0.886
Comorbidities			
Diabetes mellitus	15 (7.5%)	18 (21.4%)	0.002
Chronic obstructive pulmonary disease	12 (6.0%)	13 (15.5%)	0.019
Hypertension	48 (23.9%)	33 (39.3%)	0.010
Coronary Disease	13 (6.5%)	6 (7.1%)	0.599
Chronic Heart Failure	13 (6.5%)	13 (15.5%)	0.023
Chronic Kidney Disease (moderate to severe)[a]	14 (7.0%)	17 (20.2%)	0.003
Malignancy (solid organ or haematologic)	29 (14.4%)	7 (8.3%)	0.176
Immunosuppressive therapy	11 (5.5%)	3 (3.6%)	0.764
Obesity (BMI >30 kg/m^2)	51 (25.4%)	31 (36.9%)	0.062
Charlson Co-morbidity Index	2.2 ± 2.3	3.2 ± 2.8	0.002
ICU admission data			
SAPS II upon ICU admission	37.3 ± 9.4	43.7 ± 11.5	<0.001
SOFA score upon ICU admission	8.4 ± 3.0	9.5 ± 3.5	0.014
Prior surgery	103 (51.2%)	43 (51.2%)	1.000
AKI upon ICU admission	32 (15.9%)	23 (27.4%)	0.032
eGFR upon ICU admission (mL/min/1.73 m^2)	84.3 ± 30.8	65.7 ± 29.1	<0.001
eGFR <60 mL/min/1.73 m^2 upon ICU admission	42 (20.9%)	36 (42.9%)	<0.001
Albumin upon ICU admission (mg/dl)	2.8 ± 0.7	2.8 ± 0.8	0.790
Reason of admission			
Trauma	69 (34.3%)	16 (19.0%)	0.011
Medical	113 (56.2%)	54 (64.3%)	
Surgical	19 (9.5%)	14 (16.7%)	
BSI data			
ICU length of stay until BSI onset (days)	20.7 ± 22.5	15.7 ± 15.7	0.066
Type of microorganism			
K. pneumoniae[b]	109 (54.2%)	48 (57.1%)	0.696
A. baumannii[b]	66 (32.8%)	27 (32.1%)	1.000
P. aeruginosa[b]	38 (18.9%)	12 (14.3%)	0.397
Dual infection[c]	12 (6.0%)	3 (3.6%)	0.565
Type of infection			
Primary BSI	120 (59.7%)	53 (63.1%)	0.690d
Catheter-related BSI	58 (28.9%)	18 (21.4%)	
Other[e]	23 (11.4%)	13 (15.5%)	
SAPS II upon BSI onset	39.5 ± 10.2	48.6 ± 11.9	<0.001
SOFA score upon BSI onset	6.8 ± 3.2	9.6 ± 3.5	<0.001
Septic shock	58 (28.9%)	68 (81.0%)	<0.001
Maximum noradrenaline dose (μg/kg/min)	4.1 ± 7.7	24.0 ± 16.8	<0.001
Appropriate antibiotic treatment[f]	157 (78.1%)	54 (64.3%)	0.018

Data are number (%) of patients or mean ± standard deviation.
BMI: Body Mass Index, eGFR: estimated Glomerular Filtration Rate, ICU: Intensive Care Unit, SAPS II: Simplified Acute Physiology Score II, SOFA: Sequential Organ Failure Assessment.
[a]Defined as eGFR <60 mL/min/1.73 m^2 for ≥3 months; [b]Pathogen isolated from monomicrobial or polymicrobial infections; [c]Different species of carbapenem non-susceptible gram-negative bacteria; [d]As compared to all other types of infections; [e]16 VAP, nine abdominal infections, five nosocomial meningitis, four urinary tract and two skin and soft tissue infections; [f]defined as treatment by at least one active antibiotic.

Table 2b - Univariate analysis of risk factors for acute kidney injury (AKI) during the first 14 days of bloodstream infection (BSI) onset due to carbapenem non-susceptible Gram-negative bacteria.

Characteristics	*No AKI (n=201)*	*AKI (n=84)*	*P*
AKI data (during the first 14 days of BSI onset)			
Time to AKI from BSI onset (days)[g]	10.5 ± 4.5	6.4 ± 4.3	<0.001
eGFR upon BSI onset (mL/min/1.73 m^2)	97.4 ± 29.5	67.7 ± 33.5	<0.001
eGFR <60 mL/min/1.73 m^2 upon BSI onset	27 (13.4%)	40 (47.6%)	<0.001
Albumin upon BSI onset (mg/dl)	2.4 ± 0.5	2.3 ± 0.6	0.016
Antibiotic administration (during the first 14 days of BSI onset)			
Carbapenems	183 (91.0%)	80 (95.2%)	0.330
Penicillins	25 (12.4%)	8 (9.5%)	0.548
Cephalosporins	14 (7.0%)	7 (8.3%)	0.804
Colistin	164 (81.6%)	64 (76.2%)	0.331
Concomitant inhaled colistin	4 (2.0%)	3 (3.6%)	0.424
Tigecycline	81 (40.3%)	34 (40.5%)	1.000
Aminoglycosides	119 (59.2%)	51 (60.7%)	0.895
Quinolones	31 (15.4%)	9 (10.7%)	0.353
Trimethoprim/sulfamethoxazole	2 (1.0%)	1 (1.2%)	1.000
Glycopeptides	105 (52.2%)	50 (59.5%)	0.297
Piperacillin/tazobactam and vancomycin co- administration	110 (54.7%)	48 (57.1%)	0.794
Linezolid	108 (53.7%)	44 (52.4%)	0.897
Daptomycin	10 (5.0%)	6 (7.1%)	0.573
Metronidazole	16 (8.0%)	7 (8.3%)	1.000
Antifungal administration (during the first 14 days of BSI onset)			
Fluconazole	53 (26.4%)	13 (15.5%)	0.064
Voriconazole	3 (1.5%)	6 (7.1%)	0.021
Caspofungin	34 (16.9%)	13 (15.5%)	0.862
Anidulafungin	67 (33.3%)	31 (36.9%)	0.586
Micafungin	28 (13.9%)	15 (17.9%)	0.468
Liposomal Amphotericin B	21 (10.4%)	10 (11.9%)	0.683
Nephrotoxic medication (number)[h]	2.7 ± 1.0	2.8 ± 1.1	0.345
Nonsteroidal anti-inflammatory drug	24 (11.9%)	13 (15.5%)	0.442
Loop diuretics	157 (78.1%)	70 (83.3%)	0.339
Iodate contrast	45 (22.4%)	16 (19.0%)	0.635
Renin–angiotensin system blockers	20 (8.9%)	7 (11.5%)	0.621
ICU procedures (during the first 14 days of BSI onset)			
Cortisone administration	103 (51.2%)	54 (64.3%)	0.050
Parenteral nutrition	79 (39.3%)	32 (38.1%)	0.894
Enteral nutrition	159 (79.1%)	52 (61.9%)	0.005
Transfusions	0.7 ± 1.0	1.3 ± 2.0	0.001

Data are number (%) of patients or mean ± standard deviation.
BMI: Body Mass Index, eGFR: estimated Glomerular Filtration Rate, ICU: Intensive Care Unit, SAPS II: Simplified Acute Physiology Score II, SOFA: Sequential Organ Failure Assessment.
[g]Length of stay from BSI onset to development of AKI for cases and length of stay until death or day 14 for patients without AKI; [h]Nephrotoxins: Nonsteroidal anti-inflammatory drugs, loop diuretics, iodate contrast, renin-angiotensin system blockers, colistin, aminoglycosides, glycopeptides, trimethoprim/sulfamethoxazole, IV voriconazole, liposomal amphotericin B.

Table 3a - Univariate analysis of risk factors for acute kidney injury (AKI) during the first 14 days of bloodstream infection (BSI) onset due to carbapenem non-susceptible gram-negative bacteria treated by colistin.

Characteristics	*No AKI (n=164)*	*AKI (n=64)*	*P*
Demographics			
Age (years)	53.8 ± 18.2	60.1 ± 17.4	0.019
Male gender	120 (73.2%)	43 (67.2%)	0.415
Comorbidities			
Diabetes Mellitus	10 (6.1%)	14 (21.9%)	0.001
Chronic Obstructive Pulmonary Disease	7 (4.3%)	9 (14.1%)	0.017
Hypertension	39 (23.8%)	25 (39.1%)	0.032
Coronary Disease	11 (6.7%)	4 (6.3%)	1.000
Chronic Heart Failure	10 (6.1%)	11 (17.2%)	0.019
Chronic Kidney Disease (moderate to severe)[a]	8 (4.9%)	12 (18.8%)	0.003
Malignancy (solid organ or haematologic)	26 (15.9%)	5 (7.8%)	0.135
Immunosuppressive therapy	9 (5.5%)	2 (3.1%)	0.732
Obesity (BMI >30 kg/m^2)	42 (25.6%)	27 (42.2%)	0.017
Charlson Co-morbidity Index	2.1 ± 2.3	3.1 ± 2.9	0.006
ICU admission data			
SAPS II upon ICU admission	37.1 ± 9.4	42.2 ± 11.1	0.001
SOFA score upon ICU admission	8.7 ± 2.9	9.6 ± 3.5	0.044
Prior surgery	95 (53.4%)	25 (50.0%)	0.749
AKI upon ICU admission	28 (17.1%)	17 (26.6%)	0.138
eGFR upon ICU admission (mL/min/1.73 m^2)	83.5 ± 31.2	66.0 ± 28.9	<0.001
eGFR <60 mL/min/1.73 m^2 upon ICU admission	36 (22.0%)	27 (42.2%)	0.003
Albumin upon ICU admission (mg/dl)	2.8 ± 0.7	2.8 ± 0.8	0.855
Reason of admission			
Trauma	62 (37.8%)	11 (17.2%)	0.003
Medical	86 (52.4%)	44 (68.8%)	
Surgical	16 (9.8%)	9 (14.1%)	
BSI data			
ICU length of stay until BSI onset (days)	20.8 ± 22.1	18.0 ± 17.0	0.355
Type of microorganism			
K. pneumoniae[b]	90 (54.9%)	37 (57.8%)	0.767
A. baumannii[b]	53 (32.3%)	19 (29.7%)	0.753
P. aeruginosa[b]	32 (19.5%)	11 (17.2%)	0.851
Dual infection[c]	11 (6.7%)	3 (4.7%)	0.762
Type of infection			
Primary BSI	100 (61.0%)	44 (68.8%)	
Catheter-related BSI	49 (29.9%)	12 (18.8%)	0.098[d]
Othere	15 (9.1%)	8 (12.5%)	
SAPS II upon BSI onset	39.5 ± 10.0	46.8 ± 10.7	<0.001
SOFA score upon BSI onset	7.0 ± 3.3	9.3 ± 3.2	0.001
Septic shock	49 (29.9%)	52 (81.3%)	<0.001
Maximum noradrenaline dose (μg/kg/min)	4.4 ± 8.1	22.5 ± 16.3	<0.001
Appropriate antibiotic treatment[f]	139 (84.8%)	52 (81.3%)	0.551

Data are number (%) of patients or mean ± standard deviation.
BMI: Body Mass Index, eGFR: estimated Glomerular Filtration Rate, ICU: Intensive Care Unit, SAPS II: Simplified Acute Physiology Score II, SOFA: Sequential Organ Failure Assessment.
[a]Defined as eGFR <60 mL/min/1.73 m^2 for ≥3 months; [b]Pathogen isolated from monomicrobial or polymicrobial infections; [c]Different species of carbapenem non-susceptible gram-negative bacteria; [d]As compared to all other types of infections; [e]16 VAP, nine abdominal infections, five nosocomial meningitis, four urinary tract and two skin and soft tissue infections; [f]defined as treatment by at least one active antibiotic.

Table 3b - Univariate analysis of risk factors for acute kidney injury (AKI) during the first 14 days of bloodstream infection (BSI) onset due to carbapenem non-susceptible gram-negative bacteria treated by colistin.

Characteristics	*No AKI (n=164)*	*AKI (n=64)*	*P*
AKI data (during the first 14 days of BSI onset)			
Time to AKI from BSI onset (days)[g]	11.0 ± 4.2	7.0 ± 4.2	<0.001
eGFR upon BSI onset (mL/min/1.73 m^2)	98.0 ± 29.7	71.4 ± 32.4	<0.001
eGFR <60 mL/min/1.73 m^2 upon BSI onset	21 (12.8%)	28 (43.8%)	<0.001
Albumin upon BSI onset (mg/dl)	2.4 ± 0.5	2.3 ± 0.6	0.079
Antibiotic administration (during the first 14 days of BSI onset)			
Carbapenems	150 (91.5%)	61 (95.3%)	0.409
Penicillins	20 (12.2%)	7 (10.9%)	1.000
Cephalosporins	11 (6.7%)	6 (9.4%)	0.575
Concomitant inhaled colistin	4 (2.4%)	3 (4.7%)	0.404
Tigecycline	78 (47.6%)	31 (48.4%)	1.000
Aminoglycosides	108 (65.9%)	47 (73.4%)	0.343
Quinolones	26 (15.9%)	7 (10.9%)	0.407
Trimethoprim/sulfamethoxazole	2 (1.2%)	0 (0.0%)	1.000
Glycopeptides	82 (50.0%)	36 (56.3%)	0.461
Linezolid	92 (56.1%)	38 (59.4%)	0.766
Daptomycin	10 (6.1%)	4 (6.3%)	1.000
Metronidazole	13 (7.9%)	4 (6.3%)	0.785
Antifungal administration (during the first 14 days of BSI onset)			
Fluconazole	42 (25.6%)	10 (15.6%)	0.117
Voriconazole	2 (1.2%)	5 (7.8%)	0.020
Caspofungin	28 (17.1%)	11 (17.2%)	1.000
Anidulafungin	59 (36.0%)	24 (37.5%)	0.879
Micafungin	25 (15.2%)	13 (20.3%)	0.429
Liposomal Amphotericin B	20 (12.2%)	10 (15.6%)	0.516
Nephrotoxic medication (number)[h]	2.5 ± 1.0	2.7 ± 1.2	0.281
Nonsteroidal anti-inflammatory drug	24 (14.6%)	11 (17.2%)	0.684
Loop diuretics	131 (79.9%)	55 (85.9%)	0.345
Iodate contrast	38 (23.2%)	12 (18.8%)	0.593
Renin–angiotensin system blockers	17 (10.4%)	6 (9.4%)	1.000
ICU procedures (during the first 14 days of BSI onset)			
Cortisone administration	88 (53.7%)	39 (60.9%)	0.374
Parenteral nutrition	70 (42.7%)	27 (42.2%)	1.000
Enteral nutrition	131 (79.9%)	45 (70.3%)	0.159
Transfusions	0.7 ± 1.0	1.5 ± 2.1	0.001

Data are number (%) of patients or mean ± standard deviation.
BMI: Body Mass Index, eGFR: estimated Glomerular Filtration Rate, ICU: Intensive Care Unit, SAPS II: Simplified Acute Physiology Score II, SOFA: Sequential Organ Failure Assessment.
[g]Length of stay from BSI onset to development of AKI for cases and length of stay until death or day 14 for patients without AKI; [h]Nephrotoxic medication: Nonsteroidal anti-inflammatory drugs, loop diuretics, iodate contrast, renin–angiotensin system blockers, aminoglycosides, glycopeptides, trimethoprim/sulfamethoxazole, IV voriconazole, liposomal amphotericin B.

well as the deleterious effect of noradrenaline on renal blood flow and perfusion [7, 24, 26, 27]. As previously shown the depth and the duration of acute circulatory failure during sepsis is an independent determinant of AKI progression [7, 24]. We have previously published the results concerning predictors of 30-day mortality of BSI by CnS-GNB, without assessing the role of AKI on mortality [3, 4]. The present study demonstrated that AKI development was independently associated with 14-day mortality, which is in accordance with previous reports [6, 20, 28]. As previously shown, the type of pathogen did not influence the occurrence of AKI. However, concerning the 14-day mortality, *P. aeruginosa* was independently associated with mortality as compared to both *K. pneumoniae* and *A. baumannii*, most likely because of *P. aeruginosa* virulence. No specific type of infection led to AKI, but catheter-related BSI was independently associated with better survival due to rapid and efficient source control by removing the infected catheter [29].

Table 4a - Univariate analysis of predictors of 14-day mortality of bloodstream infection (BSI) due to carbapenem non-susceptible Gram-negative bacteria.

Characteristics	*Survivors (n=208)*	*Non-survivors (n=108)*	*P*
Demographics			
Age (years)	54.4 ± 18.3	60.0 ± 16.6	0.008
Male gender	151 (72.6%)	76 (70.4%)	0.694
Comorbidities			
Diabetes Mellitus	13 (7.0%)	11 (22.0%)	0.007
Chronic Obstructive Pulmonary Disease	10 (4.8%)	16 (14.8%)	0.004
Hypertension	57 (27.4%)	42 (38.9%)	0.041
Coronary Disease	11 (5.3%)	14 (13.0%)	0.026
Chronic Heart Failure	15 (7.2%)	16 (14.8%)	0.045
Chronic Kidney Disease (moderate to severe)[a]	19 (9.1%)	22 (20.4%)	0.008
Malignancy (solid organ or haematologic)	24 (11.5%)	16 (14.8%)	0.476
Immunosuppressive therapy	7 (3.4%)	8 (7.4%)	0.160
Obesity (BMI >30 kg/m^2)	62 (29.8%)	30 (27.8%)	0.794
Charlson Co-morbidity Index	2.1 ± 2.3	3.3 ± 2.7	<0.001
ICU admission data			
SAPS II upon ICU admission	38.4 ± 10.4	43.5 ± 12.2	<0.001
SOFA score upon ICU admission	8.9 ± 3.0	9.4 ± 3.7	0.199
Prior surgery	111 (53.4%)	54 (50.0%)	0.635
AKI upon ICU admission	50 (24.0%)	26 (24.1%)	1.000
eGFR upon ICU admission (mL/min/1.73 m^2)	78.8 ± 33.2	68.5 ± 31.2	0.008
eGFR <60 mL/min/1.73 m^2 upon ICU admission	60 (28.8%)	44 (40.7%)	0.043
Albumin upon ICU admission (mg/dl)	2.9 ± 0.7	2.7 ± 0.8	0.030
Reason of admission			
Trauma	67 (32.2%)	22 (20.4%)	
Medical	120 (57.7%)	65 (60.2%)	
Surgical	21 (10.1%)	21 (19.4%)	0.024

Data are number (%) of patients or mean ± standard deviation.
BMI: Body Mass Index, eGFR: estimated Glomerular Filtration Rate, ICU: Intensive Care Unit, SAPS II: Simplified Acute Physiology Score II, SOFA: Sequential Organ Failure Assessment.
[a]Defined as eGFR <60 mL/min/1.73 m^2 for ≥3 months

Table 4b - Univariate analysis of predictors of 14-day mortality of bloodstream infection (BSI) due to carbapenem non-susceptible Gram-negative bacteria.

Characteristics	*Survivors (n=208)*	*Non-survivors (n=108)*	*P*
Infection data			
Serum creatinine upon BSI onset (mg/dl)	1.1 ± 1.0	1.5 ± 1.1	0.001
eGFR upon BSI onset (mL/min/1.73 m^2)	89.9 ± 35.1	67.7 ± 37.8	<0.001
eGFR <60 mL/min/1.73 m^2 upon BSI onset	45 (21.6%)	44 (40.7%)	<0.001
Albumin upon BSI onset (mg/dl)	2.5 ± 0.6	2.2 ± 0.5	<0.001
ICU length of stay until BSI onset (days)	18.5 ± 18.4	19.0 ± 23.3	0.860
Type of microorganism			
K. pneumoniae[b]	120 (57.7%)	54 (50.0%)	0.233
A. baumannii[b]	69 (33.2%)	36 (33.3%)	1.000
P. aeruginosa[b]	26 (12.5%)	28 (25.9%)	0.004
Dual infection[c]	7 (3.4%)	10 (9.3%)	0.036
Type of infection			
Primary BSI	121 (58.2%)	69 (63.9%)	
Catheter-related BSI	63 (30.3%)	20 (18.5%)	0.031[d]
Other[e]	24 (11.5%)	19 (17.6%)	
SAPS II upon BSI onset	39.3 ± 10.5	51.0 ± 11.8	<0.001
SOFA score upon BSI onset	6.8 ± 3.2	10.3 ± 3.7	<0.001
Septic shock	65 (31.3%)	81 (75.0%)	<0.001
Maximum noradrenaline dose (µg/kg/min)	5.6 ± 10.7	19.4 ± 16.1	<0.001
AKI during the first 14 days of BSI onset	29 (14.9%)	55 (61.1%)	<0.001
Renal replacement therapy (either to chronic kidney disease AKI)	16 (7.7%)	27 (25.0%)	<0.001
Antibiotic treatment (during the first 14 days of BSI onset)			
No empiric appropriate antibiotic treatment	42 (20.2%)	44 (40.7%)	
Monotherapy[f]	107 (51.4%)	49 (45.4%)	
Combination therapyg	59 (28.4%)	15 (13.9%)	0.005h
Colistin	166 (79.8%)	88 (81.5%)	0.767
Tigecycline	82 (39.4%)	45 (41.7%)	0.718
Aminoglycosides	124 (59.6%)	62 (57.4%)	0.719
ICU procedures (during the first 14 days of BSI onset)			
Cortisone administration	103 (49.5%)	75 (69.4%)	0.001
Parenteral nutrition	76 (36.5%)	56 (51.9%)	0.011
Enteral nutrition	161 (77.4%)	65 (60.2%)	0.002
Transfusions	0.8 ± 1.3	1.1 ± 1.8	0.097

Data are number (%) of patients or mean ± standard deviation.
BMI: Body Mass Index, eGFR: estimated Glomerular Filtration Rate, ICU: Intensive Care Unit, SAPS II: Simplified Acute Physiology Score II, SOFA: Sequential Organ Failure Assessment.
[b]Pathogen isolated from monomicrobial or polymicrobial infections; cDifferent species of carbapenem non-susceptible gram-negative bacteria; [d]As compared to all other types of infections; [e]19 VAP, 11 abdominal infections, six urinary tract, five nosocomial meningitis and two skin and soft tissue infections; [f]defined as treatment by only one active antibiotic; gdefined as treatment by two or more active antibiotics; [h]as compared to no appropriate antibiotic treatment and monotherapy.

Previous studies assessing the role of colistin on AKI development were conducted before 2014, when colistin dosing regimens varied between institutions due to the absence of robust pharmacokinetic/pharmacodynamic data [9, 13, 16, 18, 25]. The majority of them showed that high colistin dose and/or administration of a loading dose led to AKI [11, 14, 16, 18, 29]. In our institution, guidelines concerning colistin's administration were introduced in late 2011, comprising of a loading dose followed by a twice daily dose as depicted in Table 1. Although colistin's dose used in the present study was considered by the aforementioned studies as high, there was no effect on AKI development. Gibson et al. and Falagas et al. also have shown that high colistin's dose led to higher cure rates, but this was not associated to higher percentages of AKI [10, 25]. Neither colistin nor other nephrotoxic medications were associated with AKI.

In accordance with the literature, obesity was an additional risk factor for AKI development [17, 20]. Gauthier et al. showed that the increase in AKI due to increased BMI was independent of the total daily dose of colistin [17]. No clear explanation for the role of obesity on colistin-induced nephrotoxicity has been proposed.

As previously shown, baseline renal impairment, as indicated by reduced eGFR upon bacteraemia's onset, was associated with higher rates of AKI in patients treated with colistin [14, 17, 19, 20]. Most likely patients with impaired renal function, even with adjusted doses, achieve higher colistin trough levels in the plasma secondary to diminished renal excretion, leading to higher exposure of the kidneys to toxic concentrations [12, 15]. This could be averted by colistin plasma level measurement, which was not available in our setting [12].

As other studies have shown, septic shock and severity of infection (as depicted by SAPS II or SOFA scores upon onset of BSI) were associated with mortality, while combination therapy led to better survival [1, 3-5]. Until the introduction in the clinical practice of the new category of second-generation beta-lactam/beta-lactamase inhibitor combinations, treatment of infections by CnS-GNB comprised mainly of colistin, aminoglycoside and tigecycline [1]. Since most data favors the utilization of combination therapy in patients at high risk of death, many patients received a combination of colistin and aminoglycosides which are both nephrotoxic [1, 5]. The simultaneous use of colistin and aminoglycoside did not increase the risk of AKI, being an important finding as resistance to last resort antibiotics (aminoglycosides, colistin, tigecycline, second-generation beta-lactam/beta-lactamase inhibitor combinations) is increasing, and the combination of both potential nephrotoxic agents might be mandatory in the near future.

This is the first study showing that the simultaneous use of colistin and voriconazole was independently associated with development of AKI. All patients receiving voriconazole had normal baseline renal function. It is noteworthy that other nephrotoxic medications (nonsteroidal anti-inflammatory drugs, loop diuretics, iodate contrast, renin-angiotensin system blockers, aminoglycosides, glycopeptides, trimethoprim/sulfamethoxazole and liposomal amphotericin B) when used simultaneously with colistin had no adverse effect in renal function. Voriconazole has been associated with AKI especially in critically ill patients due to potential toxic effects of the accumulation of the solvent vehicle sulphobutyl ether beta cyclodextrin sodium [30]. Based on these results, co-administration of voriconazole and colistin should be avoided, and probably an alternative antifungal should be used.

The main limitation of our study is its retrospective design, but it is compensated by the large number of patients included and the fact that all patients fitting the pre-determined inclusion criteria were studied. Since this study was conducted exclusively in critically ill patients, the results presented herein should not be extrapolated to other patient populations. Also, no colistin plasma levels were measured in order to elucidate the relationship between high levels and nephrotoxicity.

CONCLUSIONS

In conclusion, no increase in AKI rate was identified in patients with BSI due to CnS-GNB receiving potential nephrotoxic medications, including colistin. AKI was strongly associated with presence of septic shock, BMI and baseline renal impairment. Co-administration of colistin with voriconazole led to an increased rate of AKI, rendering their combined use problematic. In the era

of limited therapeutic options for CnS-GNB, utilization of high doses of colistin remains an effective and relative safe choice.

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Conflicts of interest
The authors declare no competing financial interests.

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