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Clinical Experience of Colistin-Glycopeptide Combination in Critically Ill Patients Infected with Gram-Negative Bacteria

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A colistin-glycopeptide combination (CGC) has been shown *in vitro* to be synergistic against multidrug-resistant Gram-negative bacteria (MDR GNB), especially *Acinetobacter baumannii*, and to prevent further resistance. However, clinical data are lacking. We carried out a retrospective multicenter study of patients hospitalized in intensive care units (ICUs) who received colistin for GNB infection over a 1-year period, to assess the rates of nephrotoxicity and 30-day mortality after treatment onset among patients treated with and without CGC for ≥48 h. Of the 184 patients treated with colistin, GNB infection was documented for 166. The main causative agents were MDR *A. baumannii* (59.6%), MDR *Pseudomonas aeruginosa* (18.7%), and carbapenem-resistant *Klebsiella pneumoniae* (14.5%); in 16.9% of patients, a Gram-positive bacterium (GPB) coinfection was documented. Overall, 68 patients (40.9%) received CGC. Comparison of patients treated with and without CGC showed significant differences for respiratory failure (39.7% versus 58.2%), ventilator-associated pneumonia (54.4% versus 71.4%), MDR *A. baumannii* infection (70.6% versus 52%), and GPB coinfection (41.2% versus 0%); there were no differences for nephrotoxicity (11.8% versus 13.3%) and 30-day mortality (33.8% versus 29.6%). Cox analysis performed on patients who survived for ≥5 days after treatment onset showed that the Charlson index (hazard ratio [HR], 1.26; 95% confidence interval [CI], 1.01 to 1.44; $P = 0.001$) and MDR *A. baumannii* infection (HR, 2.51; 95% CI, 1.23 to 5.12; $P = 0.01$) were independent predictors of 30-day mortality, whereas receiving CGC for ≥5 days was a protective factor (HR, 0.42; 95% CI, 0.19 to 0.93; $P = 0.03$). We found that CGC was not associated with higher nephrotoxicity and was a protective factor for mortality if administered for ≥5 days.

Severe infections due to Gram-negative bacteria (GNB) continue to be associated with high mortality among patients requiring admission to intensive care units (ICUs) (1). Increasing antibiotic resistance in organisms such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Klebsiella pneumoniae* is contributing to difficulties with choosing antimicrobial therapy for critically ill patients with a known or suspected infection (2). The emergence and global spread of resistance to carbapenems in GNB have forced clinicians to use old, previously discarded antibiotics, such as colistin (3). However, colistin has some important limitations, such as toxicity and a proclivity to the emergence of resistance during treatment, especially if used as monotherapy (4, 5). Given these concerns, it is clear why many clinicians have embraced combination therapy as the preferred treatment strategy for GNB infection (2, 6, 7).

Recently, a potent *in vitro* synergistic activity against multidrug-resistant (MDR) *A. baumannii* strains was observed when a glycopeptide (vancomycin or teicoplanin) was combined with colistin (8, 9). This effect likely results from the action of colistin on the *A. baumannii* outer membrane, enabling glycopeptides access to cell wall targets from which they are usually excluded. Furthermore, such a combination was shown to be active against other MDR GNB that were heteroresistant to colistin (10, 11). However, the main concern for the use of a colistin-glycopeptide combination is the potential for nephrotoxicity, and thus, to date, the evidence for its clinical efficacy is lacking. On the other hand, the concomitant use of glycopeptides and antibiotics active against GNB is not uncommon in the ICU setting, especially in the phase of empirical therapy.

We carried out a multicenter retrospective study on a cohort of critically ill patients who received a colistin-based antimicrobial treatment for a GNB infection to determine the frequency of administration of a combination including a glycopeptide for at least 48 h and the impact of the colistin-glycopeptide combination on the outcome.

MATERIALS AND METHODS

Study design and population. This was a retrospective multicenter cohort study of all adult (≥18 years) critically ill patients who received a colistin-based antimicrobial treatment during stay in an ICU over a 1-year period (from January 2010 to January 2011).

Setting. The study was conducted in three teaching tertiary care hospitals, one research institute, and one secondary care hospital, with a total of 64 surgical, 54 medical, and 36 mixed ICU beds.

Data. The following data were recorded in a preestablished form: demographic data, including age and sex; underlying diseases according to the Charlson index; date of hospitalization; date of ICU admission, reason for ICU admission, and APACHE II score at ICU admission; type of infection, pathogens isolated, and their susceptibility patterns; dates of start and end of colistin and other antibiotics administered during the ICU stay

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to treat a determined infection episode, reason for antimicrobial administration (empirical or targeted according to microbiological results), and adverse events secondary to the antimicrobial therapy; and outcome data, including length of ICU stay, length of hospital stay, and in-hospital death.

Definitions. For underlying conditions, renal disease was defined as the need for chronic renal support or the presence of a renal impairment (creatinine clearance [CL_{CR}] of <50 ml/min) at the time of hospital admission. Immunosuppression refers to patients with HIV infection, recipients of solid organ transplants, and patients receiving treatment for solid or hematological malignancy.

Diagnosis of infection was defined according to the criteria of the International Sepsis Forum (12) and was confirmed by the local investigator.

We defined multidrug resistance (MDR) as resistance to carbapenems for *A. baumannii* and resistance to ≥3 classes of antimicrobials for *P. aeruginosa* (13). For carbapenem-resistant *K. pneumoniae* (CR-KP), we refer to strains showing a reduced susceptibility to ertapenem (MIC of ≥1 mg/liter) (14).

Antibiotic administration was defined as empirical when therapy was started before microbiological results were available and as definitive treatment when antibiotics were administered according to microbiological results. We defined colistin combination treatment as the concurrent administration of colistin and other antibiotics for ≥48 h to treat a unique infection episode.

For adverse events to antibiotic therapy, all changes in clinical symptoms and signs and in laboratory values that occurred after starting antimicrobial treatment were recorded. Patients who met the risk, injury, or failure criteria of the RIFLE (risk, injury, failure, loss, and end-stage kidney disease) definition after treatment onset were considered to have nephrotoxicity (15).

Thirty-day mortality was defined as death within 30 days after start of colistin treatment.

Microbiology. Strains were identified to the species level with a Vitek 2 automated system (bioMérieux, Marcy l'Etoile, France) in all centers but one that used matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) (Bruker Daltonics). In all the centers, the MICs of beta-lactam inhibitor combinations, oxyiminocephalosporins, carbapenems, aztreonam, quinolones, and aminoglycosides were determined with a Vitek 2 system. Colistin MICs were determined using the Etest (bioMérieux) on cation-adjusted Mueller-Hinton agar. MICs were classified according to Clinical and Laboratory Standards Institute (CLSI) breakpoints.

Statistical analysis. Categorical variables are presented as absolute numbers and their relative frequencies. Quantitative variables are presented as means and standard deviations (SD) if normally distributed or as medians and interquartile ranges (IQR) if nonnormally distributed. We compared categorical variables between groups by using the Pearson chi-square and Fisher's exact tests; for the quantitative variables, the nonparametric Mann-Whitney U and Kruskal-Wallis tests were used in pairwise and multiple comparisons, respectively. A *post hoc* Bonferroni correction was made for comparisons between >2 groups. Analysis of risk factors for 30-day mortality was performed using the Cox regression model assuming proportional hazards. Because early mortality is generally associated with inadequate empirical therapy, while definitive therapy has an impact on morbidity and late mortality, and considering that in our study colistin was mostly administered as definitive therapy, and thus in many cases the early mortality was probably due to inadequate empirical therapy, patients who died within 5 days after the colistin-based treatment onset were excluded to rule out this potential bias, and the remaining patients were considered from the day of colistin treatment onset until death or hospital discharge. Variables with *P* values of <0.1 in the univariate analysis were included in the multivariate analysis, and this was also adjusted for age, sex, and the presence of Gram-positive bacterium (GPB) coinfection. Differences were considered to be significant for *P* values of <0.05. The analysis was carried out using SPSS 20.0 (SPSS, Chicago, IL).

RESULTS

Overall, 184 adult patients hospitalized in the ICU received an intravenous colistin-based antimicrobial treatment over the study period. The colistin-based therapy was started as empirical treatment in 38 patients and as definitive treatment in 146 patients. In 166 patients, an infection caused by GNB was confirmed by diagnostic testing.

The characteristics of the patients with GNB infection are shown in Table 1. Ventilator-associated pneumonia (VAP) was the most common type of infection (64.5%), followed by bloodstream infection (BSI) (19.9%). One of the five patients classified as having urinary tract infection had pyelonephritis, and the other four presented with severe sepsis. The main pathogens were MDR *A. baumannii* and MDR *P. aeruginosa*, isolated in 59.6% and 18.7% of patients, respectively. In 41 patients, a polymicrobial infection was diagnosed, with isolation of a GPB strain in 28 patients and of another GNB strain in the remaining 13 patients. GPB strains were isolated from 25 patients with MDR *A. baumannii* infection. Among these, the distribution of the coinfecting GPB pathogens was as follows: coagulase-negative staphylococci (CNS) in 12 cases, including 5 patients with primary BSI, 5 with central venous catheter (CVC)-related BSI, 1 with nosocomial meningitis, and 1 with surgical site infection (SSI); methicillin-resistant *Staphylococcus aureus* (MRSA) in 8 cases, including 5 patients with VAP, 2 with BSI secondary to lower respiratory tract (LRT) infection, and 1 with SSI; *Enterococcus* spp. in 3 patients with intra-abdominal infection; and *Corynebacterium striatum* in a patient with VAP and another with a BSI secondary to LRT infection. The other 3 GPB were isolated from three patients, with a postsurgical meningitis with isolation of MDR *P. aeruginosa* and a CNS strain, a primary BSI with isolation from blood cultures of a non-MDR *A. baumannii* strain and a CNS strain, and a VAP due to a MRSA strain and a *Morganella morganii* strain.

Overall, 68 patients (40.9%) received a colistin-glycopeptide combination: 62 with vancomycin and 6 with teicoplanin. Glycopeptides were initiated on the same day as colistin in 17 patients. In 27 patients, glycopeptides were initiated within a median of 3 days (IQR, 2 to 6 days) before colistin treatment onset. In 24 patients, glycopeptides were started within a median of 5 days (IQR, 3 to 5.7 days) after colistin treatment onset. Glycopeptides were initiated empirically and targeted to microbiological results in 58.8% and 41.2% of patients, respectively. Dosages and schedules used for colistin and glycopeptide administration are shown in Table 2.

Patients were classified into the following four groups according to antimicrobial treatment: colistin alone (36.7%), colistin-glycopeptide combination (25.3%), colistin plus another anti-GNB drug (22.2%), and colistin-glycopeptide plus another anti-GNB drug (15.6%). As shown in Table 3, the most significant difference between these groups was the presence of a GPB coinfection, which was more frequent among patients treated with combinations including a glycopeptide. Patients who received colistin plus other anti-GNB drugs had renal disease, diabetes mellitus, and VAP more commonly than those treated with other regimens.

Patients were further divided into patients who received combinations including a glycopeptide and those treated with combi-

TABLE 1 Characteristics of the study population

Characteristic[a]	No. (%) of patients[b] ($n = 166$)
Demographic data	
Age (yr) (median, IQR)	62, 46–73.2
Sex	
Male	103 (62)
Female	63 (38)
Underlying conditions	
Renal disease	42 (25.3)
Immunosuppression[c]	28 (16.9)
Diabetes mellitus	27 (16.3)
Liver disease	12 (7.2)
Congestive heart failure	11 (6.6)
Chronic obstructive pulmonary disease	9 (5.4)
Cerebrovascular disease	5 (3)
Charlson index (median, IQR)	3.5, 2–5
Reasons for admission to ICU	
Respiratory failure	84 (50.6)
Acute neurological disorder	37 (22.3)
Septic shock	26 (15.7)
Trauma/postsurgery	14 (8.4)
Cardiac arrest	5 (3)
APACHE II score (median, IQR)	20, 17–24
Type of infection	
Ventilator-associated pneumonia	107 (64.5)
Bloodstream infection	33 (19.9)
Primary	9 (5.4)
Secondary	24 (14.4)
Central venous catheter	11 (6.6)
Lower respiratory tract	10 (6)
Urinary tract	3 (1.8)
Surgical site infection	6 (3.6)
Urinary tract infection	5 (3)
Intra-abdominal infection	4 (2.4)
Etiology	
Gram-negative bacteria	
MDR *Acinetobacter baumannii*[d]	99 (59.6)
MDR *Pseudomonas aeruginosa*[e]	31 (18.7)
CR *Klebsiella pneumoniae*	24 (14.5)
Non-MDR *Acinetobacter baumannii*	13 (7.8)
Non-MDR *Pseudomonas aeruginosa*	5 (3)
ESBL-producing *Escherichia coli*	1 (0.6)
Morganella morganii	1 (0.6)
Polymicrobic infection	41 (24.7)
Gram-negative plus Gram-positive infection	28 (68.2)
Coagulase-negative staphylococci	14 (50)
Methicillin-resistant *Staphylococcus aureus*	9 (32.1)
Enterococcus spp.	3 (10.7)
Corynebacterium striatum	2 (7.1)
Gram-negative plus Gram-negative infection	13 (31.7)
CR *K. pneumoniae*	4 (30.7)
MDR *A. baumannii*	4 (30.7)
Non-MDR *A. baumannii*	3 (23.1)
Non-MDR *P. aeruginosa*	1 (7.7)
Enterobacter spp.	1 (7.7)
Antibiotic treatment	
Colistin alone	61 (36.7)
Colistin plus glycopeptides	42 (25.3)
Colistin plus carbapenems	21 (12.7)
Colistin plus tigecycline	12 (7.2)
Colistin plus aminoglycosides	3 (1.8)
Colistin plus rifampin	1 (0.6)
Colistin plus glycopeptides plus carbapenems	17 (10.2)
Colistin plus glycopeptides plus aminoglycosides	4 (2.4)
Colistin plus glycopeptides plus rifampin	4 (2.4)
Colistin plus glycopeptides plus tigecycline	1 (0.6)
Nephrotoxicity	21 (12.7)
Outcome	
Days of ICU stay (median, IQR)	36, 18–57.5
Days of hospital stay (median, IQR)	48, 32–85
30-day mortality	52 (31.3)

[a] Abbreviations: IQR, interquartile range; MDR, multidrug resistant; CR carbapenem resistant; ESBL, extended-spectrum beta-lactamase.
[b] Unless indicated otherwise.
[c] Immunosuppression refers to patients with HIV infection, recipients of solid organ transplants, and patients receiving treatment for solid or hematological malignancy.
[d] All these strains were resistant to carbapenems and susceptible to colistin.
[e] All these strains were resistant to ≥3 different classes of antibiotics.

nations without glycopeptides (Table 4). Significant differences were found for respiratory failure as the cause of ICU admission (39.7% versus 58.2%; $P = 0.03$), VAP (54.4% versus 71.4%; $P = 0.03$), BSI (27.9% versus 14.3%; $P = 0.05$), isolation of MDR *A. baumannii* (70.6% versus 52%; $P = 0.02$), and GPB coinfection (41.2% versus 0%; $P < 0.001$). There were no differences for nephrotoxicity and outcome (Table 4). The same analysis was further done only for patients with MDR *A. baumannii* infection (Table 5). Significant differences were found for VAP (58.3% versus 82.4%; $P = 0.01$), BSI (22.9% versus 7.8%; $P = 0.05$), and GPB coinfection (52% versus 0%; $P < 0.001$).

TABLE 2 Schedules and dosages of colistin and glycopeptide intravenous administration

Drug and parameter	Value
Colistin[a] ($n = 166$)	
No. (%) of patients receiving loading dose[b]	12 (7.2)
Dosage (MU/day) (median, IQR)	6, 4–8
Vancomycin ($n = 62$)	
No. (%) of patients receiving loading dose[c]	19 (30.6)
No. (%) of patients receiving continuous infusion	40 (64.5)
No. (%) of patients receiving intermittent infusion	22 (35.5)
Dosage (g/day) (median, IQR)	2, 2–2
Teicoplanin ($n = 6$)	
No. (%) of patients receiving loading dose	6 (100)
Dosage (mg/day) (median, IQR)	400, 400–400

[a] Colistin was administered as colistimethate sodium (CMS) (Colomycin; Forest Laboratories UK LTB, Bextley, United Kingdom) dissolved in 100 ml of sterile saline and was administered over 30 min.
[b] The loading dose was 9 MU in 8 patients and 4.5 MU in 4 patients.
[c] The loading dose was 15 mg/kg, administered over 60 min, for all patients.

TABLE 3 Comparison of patients by treatment[a]

Parameter	Value				*P* value
	Colistin alone ($n = 61$)	Colistin-glycopeptide ($n = 42$)	Colistin plus other anti-GNB drugs ($n = 37$)	Colistin-glycopeptide plus other anti-GNB drugs ($n = 26$)	
Age (yr) (median, IQR)	65, 45.5–75.5	68, 46.5–67.5	56.5, 45–67.5	55, 39.2–74.7	0.27
No. (%) of males	35 (57.4)	28 (66.7)	25 (67.6)	15 (57.7)	0.66
No. (%) of patients with comorbidity					
Renal disease	11 (18)	8 (19)	16 (43.2)	7 (26.9)	0.03
Immunosuppression	7 (11.5)	11 (26.2)	5 (13.5)	5 (19.2)	0.24
Diabetes mellitus	10 (16.4)	2 (4.8)	10 (27)	5 (19.2)	0.04
Charlson index (median, IQR)	3, 2–5	3, 1–5	4, 2.5–6	4, 1–6	0.13
No. (%) of patients with reason for ICU admission					
Respiratory failure	37 (60.7)	16 (38.1)	20 (54.1)	11 (42.3)	0.11
Septic shock	9 (14.8)	9 (21.4)	5 (13.5)	3 (11.5)	0.72
Acute neurological disorder	8 (13.1)	12 (28.5)	9 (24.3)	8 (30.8)	0.14
Trauma/surgery	7 (11.5)	4 (9.5)	0	3 (11.5)	0.22
APACHE II score at ICU admission (median, IQR)	20, 18–23	21, 14.5–25	20, 17–23.5	24, 14–26.5	0.78
No. (%) of patients with type of infection					
VAP	40 (65.6)	26 (61.9)	30 (81.1)	11 (42.3)	0.02
BSI	10 (16.4)	10 (23.8)	4 (10.8)	9 (34.6)	0.10
No. (%) of patients with etiology					
MDR *A. baumannii*	29 (47.5)	30 (71.4)	22 (59.5)	18 (69.2)	0.07
MDR *P. aeruginosa*	14 (23)	5 (11.9)	7 (18.9)	5 (19.2)	0.58
CR-KP	13 (21.3)	5 (11.9)	5 (13.5)	1 (3.8)	0.18
GPB plus GNB coinfection	0	16 (38.1)	0	12 (46.2)	<0.001
No. (%) of patients with nephrotoxicity	8 (13.1)	3 (7.1)	5 (13.5)	5 (19.2)	0.52
Outcomes					
Days of ICU stay (median, IQR)	34, 19–52.5	39.5, 17.2–64.2	32, 16–54.5	43, 22.5–75.2	0.53
Days of hospital stay (median, IQR)	44, 31.5–78.5	62, 33.5–99.2	54, 26–84.5	51, 37.2–92	0.49
No. (%) of patients with 30-day mortality	17 (27.9)	14 (33.3)	12 (32.4)	9 (34.6)	0.90

[a] Abbreviations: IQR, interquartile range; ICU, intensive care unit; VAP, ventilator-associated pneumonia; BSI, bloodstream infection; MDR, multidrug resistant; CR-KP, carbapenem-resistant *Klebsiella pneumoniae*; GPB, Gram-positive bacteria; GNB, Gram-negative bacteria.

Overall, 52 patients (31.3%) died within 30 days after the initiation of colistin treatment, among whom 12 patients died within 5 days after the treatment onset. Univariate analysis of risk factors for 30-day mortality showed that a higher Charlson index, a higher APACHE II score at ICU admission, and infection due to MDR *A. baumannii* were associated with a poor outcome, whereas receiving a drug combination with a glycopeptide for at least 5 days was associated with a better outcome. After controlling for age, sex, and coinfection with GPB, the multivariate analysis showed a higher Charlson index and MDR *A. baumannii* as independent risk factors for mortality, whereas a drug combination with a glycopeptide for ≥5 days remained a protective factor (Table 6). Overall, 23 patients received the colistin combination treatment for fewer than 5 days, glycopeptides were discontinued for de-escalation therapy according to microbiological results in 21 cases, 1 patient died within 3 days of colistin-glycopeptide treatment onset (he was excluded from the analysis), and the remaining patient died within 4 days of glycopeptide and 5 days of colistin treatment onset (he was included in the analysis). In any patient, the combination treatment was stopped for nephrotoxicity or other adverse events.

Overall, it was necessary to discontinue the antibiotic treatment because of nephrotoxicity in 4 patients who received colistin monotherapy, after 5, 9, 20, and 30 days from treatment onset.

Risk factors for 30-day mortality were also analyzed among only patients infected with MDR *A. baumannii*. The Charlson index and APACHE II score were associated with poor outcomes, although not significantly by multivariate analysis, and combination with a glycopeptide for ≥5 days was confirmed to be a protective factor (Table 7). However, when we carried out the analysis only on patients with MDR *A. baumannii* infection, excluding patients with GPB coinfection, the only variable that remained associated with a worse outcome in the multivariate analysis was the APACHE II score (hazard ratio [HR], 1.08; 95% confidence interval [CI], 1.02 to 1.14; $P = 0.005$).

DISCUSSION

We found that the combination of colistin with glycopeptides was not uncommon in critically ill patients treated for Gram-negative infection, especially among those coinfected with Gram-positive bacteria. The rate of nephrotoxicity was low in our study, and there were no differences between patients treated with and without glycopeptides. Furthermore, combination treatment with colistin and a glycopeptide for at least 5 days was a factor independently associated with better outcomes among all the patients and among those with only MDR *A. baumannii* infection.

Delivering an appropriate empirical antimicrobial therapy is critical for the outcome of infectious diseases, especially among

TABLE 4 Comparison of patients who received colistin-based antimicrobial treatments with and without glycopeptides[a]

Parameter	Value		*P* value
	With glycopeptides ($n = 68$)	Without glycopeptides ($n = 98$)	
Age (yr) (median, IQR)	57, 45–71.5	65.5, 46.7–76	0.06
No. (%) of males	43 (63.2)	60 (61.2)	0.87
No. (%) of patients with comorbidity			
Renal disease	15 (22.1)	27 (27.6)	0.47
Immunosuppression	16 (23.5)	12 (12.2)	0.06
Diabetes mellitus	7 (10.3)	20 (20.4)	0.09
Charlson index (median, IQR)	3.5, 1–5	3.5, 2–5	0.58
No. (%) of patients with reason for ICU admission			
Respiratory failure	27 (39.7)	57 (58.2)	0.03
Acute neurological disorder	20 (29.4)	17 (17.3)	0.08
Septic shock	12 (17.6)	14 (14.3)	0.66
Trauma/surgery	7 (10.3)	7 (7.1)	0.57
APACHE II score at ICU admission (median, IQR)	22, 14–26	20, 18–23	0.34
No. (%) of patients with type of infection or etiology			
VAP	37 (54.4)	70 (71.4)	0.03
BSI	19 (27.9)	14 (14.3)	0.05
MDR *A. baumannii*	48 (70.6)	51 (52)	0.02
MDR *P. aeruginosa*	10 (14.7)	21 (21.4)	0.32
CR *K. pneumoniae*	6 (8.8)	18 (18.4)	0.12
GPB plus GNB coinfection	28 (41.2)	0	<0.001
No. (%) of patients with nephrotoxicity	8 (11.8)	13 (13.3)	0.82
Outcomes			
Days of ICU stay (median, IQR)	42, 19–67.7	33, 43.5 -53.2	0.28
Days of hospital stay (median, IQR)	57, 34.2–92	44.5, 30.7–79.5	0.14
No. (%) of patients with 30-day mortality	23 (33.8)	29 (29.6)	0.61

[a] Abbreviations: IQR, interquartile range; ICU, intensive care unit; VAP, ventilator-associated pneumonia; BSI, bloodstream infection; MDR, multidrug resistant; CR, carbapenem resistant; GPB, Gram-positive bacteria; GNB, Gram-negative bacteria.

critically ill patients. Several guidelines addressed this important issue and recommended choosing empirical therapy, taking into account the patient risk factors for harboring an MDR pathogen and the local ICU epidemiology (16, 17). The predisposing conditions for MDR Gram-positive and Gram-negative bacterial infections are partially similar, such as, among others, previous treatment with broad-spectrum antibiotic therapy, underlying renal disease, and prior colonization; thus, it is not uncommon for clinicians to start with a wide-spectrum antimicrobial therapy and then streamline it according to the microbiological results. In accord with this approach, we found that in our study, 40.9% of patients received a combination therapy active against both MDR GNB and GPB, and in most cases (58.8%) the anti-GPB drug was administered in an empirical manner.

The increasing carbapenem resistance rate among GNB has revitalized the use of colistin, a cationic antimicrobial peptide originally introduced for clinical use in the late 1950s but abandoned in the early 1980s because of concerns for nephrotoxicity (18). Rates of nephrotoxicity vary from approximately 50% in older studies to <20% in recent reports (15, 18, 19). We confirmed the latter data, finding an overall rate of nephrotoxicity of 12.7% that rose to 19.2% in patients treated with combinations including colistin, a glycopeptide, and another anti-GNB drug. The high level of hydration and close monitoring of renal function in the ICU setting may explain the better tolerance of nephrotoxic drugs in critically ill patients.

Another concern with the use of colistin is the risk of developing antibiotic resistance during treatment, especially if it is used as monotherapy (4, 5). To prevent this occurrence, some authors have proposed combining colistin with other drugs for treatment of severe infections due to MDR GNB (20). One of the combinations proposed is that of colistin plus a glycopeptide, due to the activity of glycopeptides on the cell wall after overcoming the outer membrane. This combination has been tested *in vitro* and in animal models against MDR GNB, especially *A. baumannii*, and shown to be synergistic and effective against colistin-resistant strains and to prevent the further development of colistin resistance (8, 9, 11, 21). However, due to the concern of nephrotoxicity, clinical data are not yet available. We found that in critically ill patients treated with colistin for a confirmed GNB infection, the combination with a glycopeptide during ≥48 h was not associated with higher nephrotoxicity. Furthermore, combination with a glycopeptide for ≥5 days was a protective risk factor for 30-day mortality. This result may be due partially to the large proportion of patients coinfected with a GPB, mainly among those with MDR *A. baumannii* infection.

Predictors of mortality in our study are in accordance with the results of the EPIC II study, which showed infection with *A. baumannii* to be a greater risk for hospital death among 14,414 ICU patients worldwide (1).

Our study has some limitations. For example, due to the retrospective design, we could not analyze the impact of the recent

TABLE 5 Comparison of patients with MDR *A. baumannii* infection who received colistin-based antimicrobial treatments with and without glycopeptides[a]

Parameter	Value		*P* value
	With glycopeptides ($n = 48$)	Without glycopeptides ($n = 51$)	
Age (yr) (median, IQR)	57, 45–71.5	66, 45–76	0.24
No. (%) of males	30 (62.5)	32 (62.7)	1
No. (%) of patients with comorbidity			
Renal disease	12 (25)	17 (33.3)	0.38
Immunosuppression	13 (27.1)	9 (17.6)	0.33
Diabetes mellitus	6 (12.5)	12 (23.5)	0.19
Charlson index (median, IQR)	4, 2–5.7	4, 2–6	0.70
No. (%) of patients with reason for ICU admission			
Respiratory failure	23 (47.9)	29 (56.9)	0.42
Acute neurological disorder	12 (25)	9 (17.6)	0.46
Septic shock	6 (12.5)	6 (11.8)	1
Trauma/surgery	6 (12.5)	5 (9.8)	0.75
APACHE II score at ICU admission (median, IQR)	22, 14–26	20, 17–23	0.25
No. (%) of patients with type of infection			
VAP	28 (58.3)	42 (82.4)	0.01
BSI	11 (22.9)	4 (7.8)	0.05
GPB plus GNB coinfection	25 (52.1)	0	<0.001
No. (%) of patients with nephrotoxicity	5 (10.4)	8 (15.7)	0.55
Outcomes			
Days of ICU stay (median, IQR)	44.5, 18–67.7	30, 16–53	0.19
Days of hospital stay (median, IQR)	52, 38.2–87.7	38, 22–63	0.08
No. (%) of patients with 30-day mortality	20 (41.7)	18 (35.3)	0.54

[a] Abbreviations: IQR, interquartile range; ICU, intensive care unit; VAP, ventilator-associated pneumonia; BSI, bloodstream infection; GPB, Gram-positive bacteria; GNB, Gram-negative bacteria.

therapeutic schemes proposed for colistin (19, 22) on the outcome and safety. Sequential diagnostic testing to determine microbiological eradication and to exclude the development of further resistance was not systematically done, so we could not analyze the impact of the combination of colistin and a glycopeptide on the timing to microbiological cure and the prevention of colistin resistance. The serum levels of glycopeptides were not recorded, so we could not establish their impact on outcome and safety.

TABLE 6 Cox regression analysis of risk factors for 30-day mortality[a]

Factor	Univariate analysis		Multivariate analysis[b]	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age	1.01 (0.99–1.03)	0.18		
Male sex	1.34 (0.71–2.50)	0.36		
Charlson index	**1.30 (1.14–1.48)**	**<0.001**	**1.26 (1.01–1.44)**	**0.001**
APACHE II score	1.05 (1.00–1.09)	0.03		
VAP	1.28 (0.66–2.49)	0.46		
BSI	0.80 (0.35–1.82)	0.60		
MDR *A. baumannii*	**2.20 (1.10–4.41)**	**0.03**	**2.51 (1.23–5.12)**	**0.01**
MDR *P. aeruginosa*	0.42 (0.15–1.18)	0.10		
CR *K. pneumoniae*	0.73 (0.28–1.87)	0.52		
Coinfection with GPB	0.63 (0.24–1.60)	0.33		
Colistin alone	0.95 (0.49–1.82)	0.87		
Colistin plus a glycopeptide	0.93 (0.45–1.99)	0.84		
Colistin plus other anti-GNB drugs	0.99 (0.46–2.15)	0.98		
Colistin plus other anti-GNB drugs plus a glycopeptide	1.19 (0.55–2.59)	0.65		
Combination including a glycopeptide for ≥48 h	1.05 (0.56–1.96)	0.86		
Days of combination with a glycopeptide	0.95 (0.89–1.01)	0.09		
Combination with a glycopeptide for ≥5 days	**0.47 (0.22–1.02)**	**0.05**	**0.42 (0.18–0.93)**	**0.03**
Nephrotoxicity	0.63 (0.22–1.77)	0.38		

[a] Abbreviations: VAP, ventilator-associated pneumonia; BSI, bloodstream infection; MDR, multidrug resistant; CR, carbapenem resistant; GPB, Gram-positive bacteria; GNB, Gram-negative bacteria. Data in bold are statistically significant.
[b] The multivariate analysis was adjusted for all variables with *P* values of ≤0.1 in the univariate analysis and for age, sex, and the presence of coinfection with GPB.

TABLE 7 Cox regression analysis of risk factors for 30-day mortality among patients with infection due to MDR *A. baumannii*[a]

Parameter	Univariate analysis		Multivariate analysis[b]	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age	1.01 (0.99–1.03)	0.16		
Male sex	1.55 (0.75–3.23)	0.24		
Charlson index	**1.27 (1.08–1.48)**	**0.003**	**1.18 (0.99–1.39)**	**0.06**
APACHE II score	**1.06 (1.01–1.11)**	**0.01**	**1.05 (0.99–1.11)**	**0.97**
VAP	0.92 (0.42–2.03)	0.84		
BSI	1.56 (0.65–3.93)	0.31		
Coinfection with a GPB	0.46 (0.17–1.21)	0.12		
Colistin alone	1.34 (0.61–2.95)	0.46		
Colistin plus a glycopeptide	0.90 (0.41–1.98)	0.79		
Colistin plus other anti-GNB drugs	0.67 (0.23–1.92)	0.45		
Colistin plus other anti-GNB drugs plus a glycopeptide	1.11 (0.47–2.60)	0.81		
Combination including a glycopeptide for ≥48 h	0.98 (0.47–2.05)	0.97		
Days of combination with a glycopeptide	0.94 (0.88–1.01)	0.09		
Combination with a glycopeptide for ≥5 days	**0.44 (0.19–0.99)**	**0.05**	**0.41 (0.17–0.98)**	**0.04**
Nephrotoxicity	0.61 (0.18–2.02)	0.42		

[a] Abbreviations: VAP, ventilator-associated pneumonia; BSI, bloodstream infection; GPB, Gram-positive bacteria; GNB, Gram-negative bacteria. Data in bold are statistically significant.
[b] The multivariate analysis was adjusted for age, sex, Charlson index, APACHE II score, coinfection with GPB, and combination with a glycopeptide for ≥5 days.

We concluded that the use of a colistin-glycopeptide combination in critically ill patients with Gram-negative infections was common and was not associated with higher nephrotoxicity in our cohort. Furthermore, when this combination lasted ≥5 days, it was associated with a higher survival rate. Further prospective randomized studies are needed to confirm our findings.

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