Efficacy of loading dose of colistin in *Acinetobacter baumannii* ventilator-associated pneumonia

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SUMMARY

Colistin loading dose (LD) has been postulated as an advance in therapy. The clinical, microbiological effectiveness and nephrotoxicity of adding an LD to systemic colistin in ventilator-associated pneumonia (VAP) caused by multidrug-resistant (MDR) *Acinetobacter baumannii* remain unknown. In this quasi-experimental study, the efficacy, outcomes and nephrotoxicity in 30 adults who received intravenous colistin with LD for MDR *A. baumannii* ventilator-associated pneumonia were compared with 22 in absence of LD. Adding LD, the clinical cure rate at 14 days of therapy increased from 47.6% to 56.7% (p>0.397). No significant differences in bacteriological clearance (80 vs 81%), ICU mortality (50% vs 54.2%) or ICU length of stay (median: 32 vs 36 days) were identified. Mortality increased (76.2% vs 35.5%, p=0.004) in patients with nephrotoxicity, with age (median 67.0 vs. 50.0 years, p=0.002) being the only risk factor for nephrotoxicity. The nephrotoxicity rate increased from 27.3% in absence of LD to 35.3% with LD and SOFA <8, and 69.2% (p=0.065) with LD and SOFA >7. Overall, nephrotoxicity was more severe in the LD group according to RIFLE criteria (p=0.015). Adding LD to systemic colistin for MDR *A. baumannii* VAP had no significant effect on clinical cure rates, bacteriologic clearance or pre-defined outcomes. However, the nephrotoxicity rate increased with LD, with special risk in adults with high organ failure development or advanced age. Further evidence regarding the risks and benefits of LD is required. The development of newer agents and strategies is urgently needed.

Keywords: colistin, loading dose, *Acinetobacter baumannii*, ventilator-associated pneumonia, nephrotoxicity.

INTRODUCTION

The increased incidence of multidrug resistant (MDR) *Acinetobacter baumannii* has led to the search for new treatment options [1-5]. However, in recent years because of the paucity of new antibiotic developments, an old class antibiotic, colistin, has been re-evaluated for salvage therapy. On the other hand, due to the low clinical effectiveness of this old drug, optimal dosage and administration is still being investigated [6]. Recent pharmacokinetic (PK) and pharmocodynamic (PD) studies about colistin, suggested the need for a loading dose (LD) for obtaining more rapidly plasma concentrations and sufficient efficacy [7, 8]. However, there is limited data about the clinical cure rates and safety of colistin with LD [6].

In this study, we aimed to investigate the clinical and microbiological effectiveness and nephrotoxicity of colistin after LD in ventilator associated pneumonia (VAP) caused by MDR *A. baumannii*.

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PATIENTS AND METHODS

This retrospective, quasi-experimental, cohort study identified all adults (>16 years) in intensive care units (ICUs) of Erciyes University Hospital between March 2014 and May 2015. VAP caused by MDR *A. baumannii* was the leading ICU-acquired infection in this ICUs in last 15 years, as reported elsewhere [9-12].

Design

Colistin has been used in our hospital since 2010. According to the knowledge of recent papers about its PK/PD properties, after 2013, it was administered with a LD for therapy of infections in the ICU. In this study, we compared the clinical and bacteriological response and colistin-related nephrotoxicity in patients receiving intravenous colistin with LD for the treatment of MDR *A. baumannii* VAP with patients previously treated without LD [13, 14]. To exclude the impact of severity of illness bias, patients were grouped according to the admission Sequential Organ Failure Assessment (SOFA) score. VAP was defined according to the criteria of the 2005 American Thoracic Society Guidelines [15]. Only patients with monomicrobial VAP and without co-infection were included into the study. Patients with renal impairment were excluded from the study. Patients treaed with inhaled colistin were excluded from the study. We recorded patients demographic characteristics; underlying disease, SOFA score, severity of sepsis, length of ICU stay, occurrence of nephrotoxicity. Sepsis was defined according to 2012 International Guidelines for Management of Severe Sepsis and Septic Shock [16]. The records of the patients were accessed from the surveillance data of the Infection Control Committee. This study was approved by the ethics committee of Erciyes University (date 20.02.2015, number 2015/99).

Identification of MDR

The identification of the isolates as *A. baumannii* was performed using Phoenix microscan system which is FDA (the United States Food and Drug Administration) approved for this use in clinical laboratories with recommended practices. The antimicrobial susceptibility was determined using the Kirby-Bauer disk diffusion test according to the Clinical and Laboratory Standards Institute (CLSI) (formerly NCCLS) [17]. *A. baumannii* isolates resistant to more than three classes of antibiotics were defined as multidrug resistant (MDR) [18]. The antimicrobial susceptibility test included aminoglycosides, anti-pseudomonal penicillins, carbapenems, cephalosporins, quinolones, beta- lactam/beta-lactamase inhibitors, colistin and tigecycline.

Colistin administration

Colistimethate sodium (Colimycin, the vial content of 150 mg colistin base activity, approximately equivalent to 5 MU, Kocak Farma) has been used. Patients in control group had received colistin 150 mg every 12 h. In LD group, patients received colistin with a loading dose of 300 mg, administered over 30 minutes in 100 ml of saline, and after 12 h followed by 150 mg every 12 h maintenance dose.

Efficacy and nephrotoxicity evaluation

The clinical and bacteriological response were evaluated on the 5th and 14th day. On the fifth day of the therapy, subsidence of symptoms and signs (fever, purulent respiratory secretions, resolution in oxygenation, etc.) of VAP without an additional antimicrobial agent for VAP, was defined as a good response; progression of symptoms, signs and prescription of antimicrobial agents were defined as a poor response. At the end of the therapy, resolution of the symptoms and signs (fever, purulent respiratory secretions, resolution in oxygenation, etc.) of VAP with or without an improvement or lack of significant progression of radiographic findings by the end of therapy were defined as a clinical cure; the persistence of symptoms and signs or recurence of VAP after the discontinuation of colistin therapy were defined as a clinical failure. Bacteriological clearance was defined as eradication of MDR *A. baumannii* at the end of the therapy, and bacteriological failure was defined as persistance of *A. baumannii* on follow up culture despite colistin therapy [19]. Creatinine clearance was calculated every other day using the equation of Cockcroft [20]. The criteria for colistin related nephrotoxicity was defined using RIFLE criteria (Risk, Injury, Failure, Loss, End stage kidney disease) [21].

Statistical analysis

The collected information was processed using version by 20.0 of the Statistical Package for Social

Sciences (SPSS) for Windows. The Shapiro-Wilk test was performed to check the normality assumption of the data. The Mann-Whitney U-test was used for the comparison of continuous variables. In order to identify the predictors of clinical cure, univariate and multivariate logistic regression analysis were used to control for the effects of confounding variables. Relative risk (RR) and their 95% confidential intervals (CIs) were calculated. All the analyses were performed with the level of significance set at $p<0.05$.

RESULTS

Patient characteristics

In this study, a total of 52 patients with MDR *A. baumannii* VAP were evaluated. The median age of

Table 1 - Demographic and clinical data of patients.

Variables	*Patients with SOFA ≤7*			*Patients with SOFA >7*			*Overall patients*		
	Colistin with LD (n=17) n (%)	*Colistin without LD* (n=10) n (%)*	*p*	*Colistin with LD (n=13) n (%)*	*Colistin without LD* (n=12) n (%)*	*p*	*Colistin with LD (n=30) n (%)*	*Colistin without LD* (n=22) n (%)*	*p*
Age in years, mean±SD or median (range)	64.0 (16-85)	53.4±22.4	1.000	56.0±16.8	56.0±21.6	1.000	61.0 (16-85)	61.5 (20-87)	0.966
Male gender	7 (41.2)	6 (60.0)	0.345	7 (53.8)	7 (58.3)	0.821	14 (46.7)	13 (59.1)	0.376
Underlying disease									
Diabetes mellitus	3 (17.6)	0 (0.0)	0.274	3 (23.1)	1 (8.3)	0.593	6 (20.0)	1 (4.5)	0.216
Chronic renal disease	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-
Chronic liver disease	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-
Chronic cardiac disease	1 (5.9)	0 (0.0)	1.000	3 (23.1)	1 (8.3)	0.593	4 (13.3)	1 (4.5)	0.381
Chronic obstructive lung disease	4 (23.5)	4 (40.0)	0.415	4 (30.8)	4 (33.3)	1.000	8 (26.7)	8 (36.4)	0.454
Malignancy	1 (5.9)	0 (0.0)	1.000	4 (30.8)	2 (16.7)	0.645	5 (16.7)	2 (9.1)	0.685
Chemotherapy	1 (5.9)	0 (0.0)	1.000	0 (0.0)	0 (0.0)	-	1 (3.3)	0 (0.0)	1.000
Steroid	4 (23.5)	5 (50.0)	0.219	3 (23.1)	4 (33.3)	0.673	7 (23.3)	9 (40.9)	0.175
Trauma	4 (23.5)	3 (30.0)	1.000	1 (7.7)	4 (33.3)	0.160	5 (16.7)	7 (31.8)	0.200
Severity of infection									
Sepsis Severe sepsis Septic shock Multi organ failure	9 (52.9) 5 (29.4) 3 (17.6) 0 (0.0)	4 (40.0) 4 (40.0) 2 (20.0) 0 (0.0)	0.872	6 (46.2) 5 (38.5) 2 (15.4) 0 (0.0)	1 (8.3) 9 (75.0) 2 (16.7) 0 (0.0)	0.154	15 (50.0) 10 (33.3) 5 (16.7) 0 (0.0)	5 (22.7) 13 (59.1) 4 (18.2) 0 (0.0)	0.126
Previous antibiotic use	17 (100)	10 (100)	-	13 (100)	10 (83.3)	0.125	30 (100)	20 (90.9)	0.174
Hospital admission before ICU admission	10 (58.8)	7 (70.0)	0.561	4 (30.8)	3 (25.0)	1.000	14 (46.7)	10 (45.5)	0.931
Antibiotic used in combination									
Carbapenem	7 (41.2)	4 (40.0)	1.000	7 (53.8)	3 (25.0)	0.226	14 (46.7)	7 (31.8)	0.281
Sulbactam	3 (17.6)	2 (20.0)	1.000	0 (0.0)	9 (75.0)	0.001	3 (10.0)	11 (50.0)	0.002
Quinolone	0 (0.0)	2 (20.0)	0.128	2 (15.4)	0 (0.0)	0.480	2 (6.7)	2 (9.1)	1.000
Aminoglycoside	0 (0.0)	2 (20.0)	0.128	0 (0.0)	2 (16.7)	0.220	0 (0.0)	4 (18.2)	0.027
Glycopeptide	5 (29.4)	3 (30.0)	1.000	5 (38.5)	4 (33.3)	1.000	10 (33.3)	7 (31.8)	0.908
Tigecycline	2 (11.8)	1 (10.0)	1.000	1 (7.7)	0 (0.0)	1.000	3 (10.0)	1 (4.5)	0.629

*LD: Loading dose.

patients was 61(16-87) years and 27 (51.9%) were male. The median SOFA score was seven and VAP was observed on the median 13th (IQR 3-6) day of mechanical ventilation. All MDR *A. baumannii* were isolated from endotracheal aspirate (>10^5). Carbapenem resistance rate was 100%, but all the isolates were susceptible to colistin (MIC ≤ 2 mg/L). Moreover, 32 (66.7%) isolates were resistant to tigecycline.

Thirty patients received colistin with LD compared with 22 controls (without LD). All these patients received colistin as directed therapy. Patients were grouped according to the median SOFA score. The demographic and clinical data of patients are shown in Table 1. Eleven (21.2%) patients had concomitant bacteremia. The demographic characteristics were not statistically significant between case and control patients. Thirty-two (61.5%) patients had severe sepsis or septic shock on the date of VAP. Patients in control group had received sulbactam and aminoglycoside in combination with intravenous colistin more commonly than those treated with colistin LD (p<0.05).

Outcomes

The clinical and bacteriological outcomes for the two groups are summarized in Table 2. On the fifth day of therapy, 36.7% of patients in colistin with LD group and 54.5% of controls had a good response (p=0.200). Thirty patients in colistin with LD group and 21 controls completed 14-day course of therapy. Clinical cure rates were 56.7% and 47.6% (p=0.397), respectively. The bacteriological clearance rates were 80.0% and 81.0% in the colistin with LD group and controls, respectively. Nephrotoxicity was observed within a median days of 7 (IQR 3-19) in 21 (40.4%) patients. Nine patients required renal replacement therapy. The nephrotoxicity rate was numerically higher in colistin with LD group (50.0%) than control group (27.3%) (p=0.099). When the patients were grouped according to the severity SOFA score, the difference was more prominent [35.3% with

Table 2 - Clinical and microbiological evaluation of patients

	Patients with SOFA ≤7			*Patients with SOFA >7*			*Overall patients*			
On the 5th day of therapy	*Colistin with LD* (n=17) n (%)	*Colistin without LD* (n=10) n (%)	*p*	*Colistin with LD* (n=13) n (%)	*Colistin without LD* (n=12) n (%)	*p*	*Colistin with LD* (n=30) n (%)	*Colistin without LD* (n=22) n (%)	*Univariate analysis OR (95%CI for odds)*	*p*
Good response Poor response	7 (41.2) 10 (58.8)	5 (50.0) 5 (50.0)	0.706	4 (30.8) 9 (69.2)	7 (58.3) 5 (41.7)	0.238	11 (36.7) 19 (63.3)	12 (54.5) 10 (45.5)	2.073 (0.676-6.356)	0.200
On the 14th day of therapy	*Colistin with LD* (n=17) n (%)	*Colistin without LD* (n=10) n (%)	*p*	Colistin with LD (n=13) n (%)	Colistin without LD (n=11) n (%)	*p*	*Colistin with LD* (n=30) n (%)	*Colistin without LD* (n=21) n (%)	*Univariate analysis OR (95%CI for odds)*	*p*
Clinical curea Clinical failure	10 (58.8) 7 (41.2)	6 (60.0) 4 (40.0)	1.000	7 (53.8) 6 (46.2)	4 (36.4) 7 (63.6)	0.444	17 (56.7) 13 (43.3)	10 (47.6) 11 (52.4)	0.695 (0.227-2.131)	0.524
Bacteriological clearance Bacteriological failure	15 (88.2) 2 (11.8)	8 (80.0) 2 (20.0)	0.613	9 (69.2) 4 (30.8)	9 (81.8) 2 (18.2)	0.649	24 (80.0) 6 (20.0)	17 (81.0) 4 (19.0)	1.063 (0.260-4.350)	1.000
Length of ICU stay, median (range)	30.0 (9-98)	35.0 (17-141)	0.440	38.0 (8-78)	38.5 (9-126)	1.000	32.0 (8-98)	36.0 (9-141)	0.989 (0.969-1.010)	0.316
Mortality	7 (41.2)	4 (40.0)	1.000	8 (61.5)	8 (66.7)	1.000	15 (50.0)	12 (54.5)	0.833 (0.277-2.511)	0.746
Nephrotoxicity	6 (35.3)	2 (20.0)	0.666	9 (69.2)	4 (33.3)	0.115	15 (50.0)	6 (27.3)	2.667 (0.819-8.679)	0.099

*LD: Loading dose.

Table 3 - Patients' relationship to RIFLE criteria in the groups.

RIFLE	*Colistin with LD (n=15) n (%)*	*Colistin without LD (n=6) n (%)*	*p*
Risk (R)	0 (0.0)	3 (50.0)	*0.015*
Injury (I)	5 (33.3)	2 (33.3)	
Failure (F)	9 (60.0)	1 (16.7)	
Loss (L)	1 (6.7)	0 (0.0)	
ESKD (E)	0 (0.0)	0 (0.0)	

LD and SOFA≤7, and 69.2% with LD and SOFA >7 (p=0.065)]. Overall, nephrotoxicity was more severe in LD group according to RIFLE criteria (p=0.015) (Table 3). However, the need for RRT was not significant in two groups and age was the only risk factor for nephrotoxicity (median age 67.0 vs 50.0, p=0.002). The median length of stay in ICU was 34.5 (IQR 8-141) days.

Predictors of clinical cure

Twenty-seven patients had clinical cure. Loading dose had no effect on clinical cure. The mortality rate was higher in patients with nephrotoxicity (76% vs. 36%), however it was not a significant risk factor for mortality. Diabetes mellitus was the only variable affecting clinical failure (OR:0.386; 95% CI: 0.266-0.561; p=0.003). Age (OR:1.083; 95% CI: 1.030-1.139; p=0.002) and clinical failure (OR:11.559; 95% CI: 1.587-84.171; p=0.016) were significant risk factors for mortality.

DISCUSSION

In this quasi-experimental study, despite clinical cure rates (56.7% vs. 47.6%) were numerically higher in the LD group than control group, the difference was not statistically significant. Furthermore, length of stay and mortality rate were not statistically different in each group. In contrast, LD exposed patients at higher risk of nephrotoxicity (using RIFLE criteria), particularly in the subset with SOFA score above 7.

In recent years, PK/PD studies have gained momentum to find the optimal dosage and administration of colistin. Colistin is a concentration-dependent antibiotic with a long half-life in critically ill patients. Recent studies revealed that standard dosage of colistin was associated with suboptimal initial steady state concentration [6]. In a recent PK modelling study, Plachouras *et al.* also showed that colistin concentrations are below the MIC breakpoints after the first few doses of the currently used dosing regimen resulting in the suboptimal initial efficacy [22]. The authors suggested the administration of a loading dose and longer dosing interval in critically ill patients to get the highest efficacy. In another PK study, investigators observed that loading doses higher than standard 160 to 240 mg increase the initial bacteria killing and recommended a loading dose of 480 to 720 mg (6 to 9 MU) in critically ill patients [23]. In our previous study, the clinical response rate at the 14th day with standard dose was 30%. Although with increasing the dose, success rate (7%) did not increase. However, we had not used loading dose and gave the high dose in short intervals [13]. After the recent published PK/PD studies, loading dose and extended-interval (12 h) administration of colistin have been used in our ICUs, but this study showed that LD did not have significant effect on the outcome.

In this study, different antibiotics were used in combination with colistin and none of them increased clinical cure rate. Also, in our experimental study, we did not found any additional effect of sulbactam in combination therapy with colistin and tigecycline in MDR *A. baumannii* sepsis [24]. In a multicenter study, colistin based combination therapy resulted in significantly higher microbiological eradication rates, relatively higher cure and 14-day survival rates and lower in-hospital mortality compared to colistin monotherapy [25]. In the literature, there are insufficient data about the superiority of combination therapy to monotherapy. Nephrotoxicity was the most common side effect of colistin (incidence 9-50%) and renal toxicity mainly included acute tubular necrosis and was considered to be dose-dependent [19, 21]. There are several risk factors for nephrotoxicity associated with colistin. It is doubtful whether LD has negative impact on the rate of colistin-related nephrotoxicity [8]. In our analysis, nephrotoxicity was more common in the LD group (50.0%), especially in severe patients with SOFA score over seven. However, it was not found statistically significant, probably due to small number of cases. In our study, age was the only significant risk factor for nephrotoxicity. In a recent study, nephrotoxici-

Table 4 - Comparison of patients with and without nephrotoxicity.

Variables	*Patients with SOFA ≤7*			*Patients with SOFA >7*			*Overall patients*		
	Nephrotoxicity (n=8) n (%)	*No Nephrotoxicity (n=19) n (%)*	*p*	*Nephrotoxicity (n=13) n (%)*	*No Nephrotoxicity (n=12) n (%)*	*p*	*Nephrotoxicity (n=21) n (%)*	*No Nephrotoxicity (n=31) n (%)*	*p*
Age in years, mean±SD or median (range)	74.5 (27-85)	50.0 (16-80)	0.003	62.3±14.2	48.7±21.1	0.060	65.5±15.9	50.0 (16-82)	0.002
APACHE II, mean±sd or median (range)	17.5 (16-22)	18.9±3.2	1.000	20.8±3.2	21.5 (15-24)	0.626	20.0±3.1	20.0 (15-25)	0.632
Male gender	2 (25.0)	11 (57.9)	0.209	6 (46.2)	8 (66.7)	0.428	8 (38.1)	19 (61.3)	0.100
SOFA, median (range)	5.5 (5-7)	6.0 (3-7)	0.856	9.0 (8-17)	10.5 (8-16)	0.347	8.0 (5-17)	7.0 (3-16)	0.309
Underlying disease									
Diabetes mellitus	1 (12.5)	2 (10.5)	1.000	4 (30.8)	0 (0.0)	0.096	5 (23.8)	2 (6.5)	0.104
Chronic renal disease	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-
Chronic liver disease	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-
Chronic cardiac disease	1 (12.5)	0 (0.0)	0.296	3 (23.1)	1 (8.3)	0.593	4 (19.0)	1 (3.2)	0.145
Chronic obstructive lung disease	3 (37.5)	5 (26.3)	0.658	6 (46.2)	2 (16.7)	0.202	9 (42.9)	7 (22.6)	0.120
Malignancy	0 (0.0)	1 (5.3)	1.000	5 (38.5)	1 (8.3)	0.160	5 (23.8)	2 (6.5)	0.104
Chemotherapy	0 (0.0)	1 (5.3)	1.000	0 (0.0)	0 (0.0)	-	0 (0.0)	1 (3.2)	1.000
Steroid	3 (37.5)	6 (31.6)	1.000	5 (38.5)	2 (16.7)	0.378	8 (38.1)	8 (25.8)	0.346
Trauma	1 (12.5)	6 (31.6)	0.389	1 (7.7)	4 (33.3)	0.160	2 (9.5)	10 (32.3)	0.093
Severity of infection									
Sepsis Severe sepsis Septic shock Multi organ failure	4 (50.0) 2 (25.0) 2 (25.0) 0 (0.0)	9 (47.4) 7 (36.8) 3 (15.8) 0 (0.0)	0.865	5 (38.5) 6 (46.2) 2 (15.4) 0 (0.0)	2 (16.7) 8 (66.7) 2 (16.7) 0 (0.0)	0.486	9 (42.9) 8 (38.1) 4 (19.0) 0 (0.0)	11 (35.5) 15 (48.4) 5 (16.1) 0 (0.0)	0.751
Previous antibiotic use	8 (100)	19 (100)	-	12 (92.3)	11 (91.7)	1.000	20 (95.2)	30 (96.8)	1.000
Hospital admission before ICU admission	5 (62.5)	12 (63.2)	1.000	6 (46.2)	1 (8.3)	0.073	11 (52.4)	13 (41.9)	0.458
Colistin with loading dose	6 (75.0)	11 (57.9)	0.666	9 (69.2)	4 (33.3)	0.115	15 (71.4)	15 (48.4)	0.099
Antibiotic used in combination									
Carbapenem	3 (37.5)	8 (42.1)	1.000	7 (53.8)	3 (25.0)	0.226	10 (47.6)	11 (35.5)	0.382
Sulbactam	2 (25.0)	3 (15.8)	0.616	3 (23.1)	6 (50.0)	0.226	5 (23.8)	9 (29.0)	0.677
Quinolone	1 (12.5)	1 (5.3)	1.000	1 (7.7)	1 (8.3)	1.000	2 (9.5)	2 (6.5)	1.000
Aminoglycoside	1 (12.5)	1 (5.3)	1.000	1 (7.7)	1 (8.3)	1.000	2 (9.5)	2 (6.5)	1.000
Glycopeptide	3 (37.5)	5 (26.3)	0.658	6 (46.2)	3 (25.0)	0.411	9 (42.9)	8 (25.8)	0.198
Tigecycline	1 (12.5)	2 (10.5)	1.000	1 (7.7)	0 (0.0)	1.000	2 (9.5)	2 (6.5)	1.000
Length of ICU stay, mean±SD or median (range)	26.4±14.3	34.0 (15-141)	0.119	39.2±17.5	32.0 (9-126)	0.437	34.3±17.2	34.0 (9-141)	0.787
Mortality	5 (62.5)	6 (31.6)	0.206	11 (84.6)	5 (41.7)	0.041	16 (76.2)	11 (35.5)	0.004

ty was found to be independently associated with IV colistin and frequent use of nebulized colistin was found to be effective for preventing nephrotoxicity in patients with a poor general condition as older age and higher APACHE II scores [26]. Nebulization of colistin without systematic administration of the drug may reduce nephrotoxicity; however, the use of nebulized colistin instead of its IV administration for the treatment of VAP caused by resistant pathogens as standard clinical care is not recommended [27, 28].

This study has several limitations. First, it is a quasi-experimental study, whose evidence level is lower than a randomized trial. A cohort design with non-equivalent control group had to be chosen among varied types of quasi-experimental designs. Furthermore, the cohort was retrospective with their inherent limitations. The sample size is small for the study objectives and small sample size may lead to insufficient power. Also, data from one center may be not generalizable to other sites.

Table 5 - Factors affecting clinical cure in 51 patients

Variables	*Clinical cure (n=27) n (%)*	*Clinical failure (n=24) n (%)*	*Univariate analysis OR (95%CI)*	*p*
Age in years (median, range)	65 (16-82)	61 (20-87)	0.991 (0.964-1.017)	0.485
APACHE II (median, range)	20 (15-25)	20 (15-25)	0.993 (0.832-1.186)	0.941
Male gender	16 (59.3)	10 (41.7)	0.491 (0.161-1.501)	0.210
Underlying disease				
Diabetes mellitus	0 (0.0)	7 (29.2)	0.386 (0.266-0.561)0.003	
Chronic renal disease	0 (0.0)	0 (0.0)	--	
Chronic liver disease	0 (0.0)	0 (0.0)	--	
Chronic cardiac disease	2 (7.4)	3 (12.5)	0.560 (0.085-3.673)	0.656
Chronic obstructive lung disease	8 (29.6)	8 (33.3)	0.842 (0.258-2.752)	0.776
Malignancy	5 (18.5)	2 (8.3)	2.500 (0.437-14.287)	0.425
Chemotherapy	1 (3.7)	0 (0.0)	-- 1.000	
Steroid	9 (33.3)	7 (29.2)	1.214 (0.370-3.990)	0.749
Trauma	6 (22.2)	5 (20.8)	1.086 (0.284-4.143)	0.904
Severity of infection				
Sepsis Severe sepsis Septic shock Multi organ failure	11 (40.7) 10 (37.0) 6 (22.2) 0 (0.0)	9 (37.5) 12 (50.0) 3(12.5) 0 (0.0)	--	0.572
Hospital admission before ICU admission	14 (51.9)	10 (41.7)	1.508 (0.498-4.567)	0.467
Loading dose	17 (63.0)	13 (54.2)	1.438 (0.469-4.410)	0.524
Previous antibiotic use	26 (96.3)	23 (95.8)	1.130 (0.067-19.118)	1.000
Antibiotic used in combination				
Carbapenem	11 (40.7)	10 (41.7)	0.963 (0.315-2.941)	0.947
Sulbactam	5 (18.5)	9 (37.5)	0.379 (0.106-1.356)	0.129
Quinolone	1 (3.7)	3 (12.5)	0.269 (0.026-2.781)	0.331
Aminoglycoside	2 (7.4)	2 (8.3)	0.880 (0.114-6.781)	1.000
Glycopeptide	9 (33.3)	7 (29.2)	1.214 (0.370-3.990)	0.749
Tigecycline	3 (11.1)	1 (4.2)	2.875 (0.279-29.677)	0.612

CONCLUSION

In conclusion, colistin with LD for MDR *A. baumannii* VAP had no significant effect on clinical cure rates, bacteriologic clearance and prognosis. In contrast, LD increased the risk of nephrotoxicity. Increased rates of complications are amplified in the context of no efficacy signal for the addition of LD. In contrast, small increases in nephrotoxicity may be less important if there is an improvement in outcomes. In essence, our manuscript is a call for:

a) higher level of evidence regarding risk-benefit of LD with special caution in patients with high organ failure development;
b) development of new agents with activity against *A. baumannii.*

Conflict of interest
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Compliance with ethics guidelines
All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013.

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