Evaluation of Acute Renal Failure After Acinetobacter Baumannii-related Ventilator-associated Event: Routine Data Base Study

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Introduction. Ventilator-associated events (VAEs) are major complications of mechanical ventilation (MV). Herein, we aimed to evaluate whether acute kidney injury (AKI) developed in patients who had been followed up with the diagnosis of Acinetobacter baumannii (AcB)-related VAE, the need for renal replacement therapy (RRT), and its relationship with mortality in patients who developed AKI due to colistin treatment.
Methods. A retrospective evaluation of 2,622 patients was conducted. Patients who developed AcB-based VAE and received parental colistin treatment were evaluated in terms of age, sex, diagnosis on intensive care unit (ICU) admission, Acute Physiology and Chronic Health Evaluation (APACHE) II score, colistin dose and treatment duration, duration of ICU stay, AKI staging according to Kidney Disease Improving Global Outcomes criteria, RRT requirement, and mortality.
Results. Eighty-five patients (3.19%) had VAEs, of whom 28 (32.9%) had AcB-related VAE. Bacterial eradication was achieved in 14 patients (50%), clinical response was achieved in 14 patients (50%), the mean colistin dose was 298.2 ± 85.5 mg/d, and mean duration of colistin treatment was 14.3 ± 8.6 days. AKI was detected as stages I, II, and III in 28.6%, 14.3%, and 28.6% of the patients; respectively. There was no difference between patients requiring RRT and those who did not in terms of the APACHE II score, bacterial eradication, clinical response to therapy, a daily dose of colistin, treatment duration, and MV duration.
Conclusion. Colistin treatment of AcB-related VAE caused AKI in 71.5% of the patients and led to serious conditions in 25% of the patients requiring RRT.

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Original Paper

INTRODUCTION

Over the last ten years, because of the limitations of ventilator-associated pneumonia (VAP) surveillance definition, there have been three definition tiers within the ventilator-associated event (VAE) algorithm: 1) ventilator-associated condition, 2) infection-related ventilator-associated complication, and 3) possible VAP.[1,2] The Centers for Disease Control and Prevention (CDC) recommended using this definition; moreover, it

includes objective criteria for ventilator-associated lower respiratory tract infections.[3]

Acinetobacter baumannii (AcB) is an opportunistic pathogen that causes serious infections, septic shock, and death in hospitalized patients. It is one of the most common nosocomial infections. It causes urinary tract infection, pneumonia, meningitis, bacteremia and sepsis, especially in patients hospitalized in the intensive care unit (ICU).[4] Although the frequency of nosocomial pneumonia caused by AcB varies regionally, approximately 20% of the pneumonia cases develop in the ICU,[5] and the mortality rate is between 30 and 70%.[6]

The increase in the frequency of infections caused by multidrug-resistant Gram-negative bacteria, especially Pseudomonas species (spp.) and Acinetobacter spp., and the challenges in their treatment have brought polymyxins back to the agenda.[7] Colistin is one of the drugs in this group, and its most important side effect is nephrotoxicity. The rate of nephrotoxicity caused by colistin in critical patients in the ICU can increase up to 40%.[8] This effect is dose-dependent and reversible.[9] Nephrotoxicity may be severe enough to warrant discontinuation of therapy, or treatment may have to be continued with renal replacement therapy (RRT).

Herein, we aimed to evaluate whether acute kidney injury (AKI) developed in ICU patients who were administered colistin for treating AcB-related VAE between January 1, 2017 and December 31, 2019, the need for RRT in patients with AKI, and the mortality rate of the patients.

MATERIALS AND METHODS

Setting and Participants

This study was approved by the local ethics committee of the hospital (date: 15.05.2020, number: 2020.05.1.09.041) between January 1, 2017, and December 31, 2019. The files and electronic medical records of the patients who were treated and followed up at the ICU of the Anesthesiology and Reanimation Clinic in a tertiary referral hospital were retrospectively evaluated.

ICU patients who were diagnosed with AcB-related VAE according to the CDC criteria for VAE[10] and developed AKI while being treated with parenteral colistin according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria[11] were included in the study (Figure 1). Patients who were younger than 18 years, pregnant, had a history of AKI, had chronic renal failure and end-stage renal disease, had intermittent and/or continuous non-invasive mechanical ventilation (MV), developed pneumonia and/or septic shock, and were treated with colistin via inhalation were excluded from the study.

Microbiological Evaluation

Sputum, endotracheal aspirate (ETA), non-bronchoscopic bronchoalveolar lavage (mini-BAL) or bronchoscopic specimens (bronchoscopic aspirate, BAL) were used for bacteriological culture. For quantitative assessment of lower respiratory tract samples obtained via a protected sterile catheter other than sputum, the threshold values were 10^5 cfu/mL for ETA and 10^4 cfu/mL for BAL and mini-BAL.

Colistin Administration

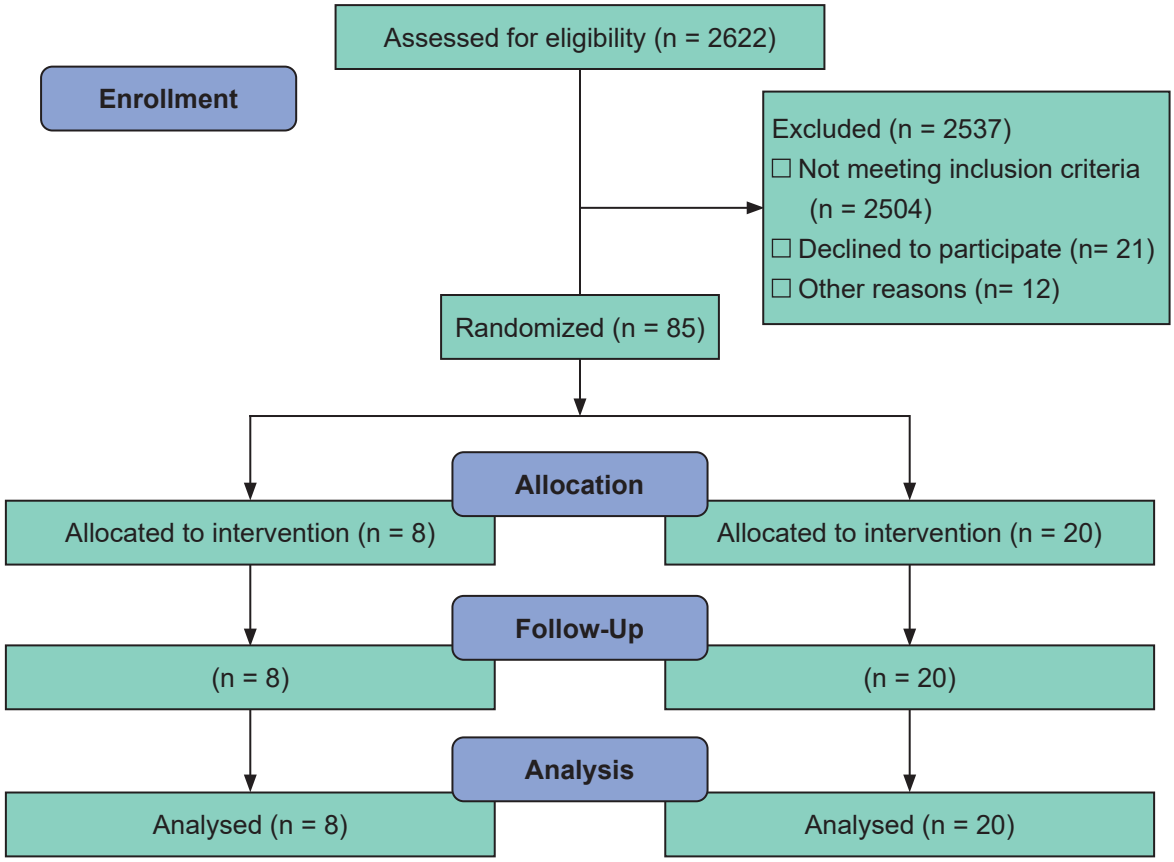
By following the normal glomerular filtration rates of the patients and calculating their ideal body weight, colistin (Lixicol®, Pharmaco, Turkey), that included 4.500.000 IU lyophilized injectable powder, was administered to the patients at a daily dose of 300 mg twice a day intravenously. One million international units of colistin is equivalent to a dose of approximately 30 mg.[12]

Assessment of Nephrotoxicity

After colistin administration on the first day, renal functions were evaluated daily according to KDIGO criteria.[11] Continuous venovenous hemodiafiltration (CVVHDF) with regional citrate anticoagulation was applied due to stage III AKI, acidosis, electrolyte imbalance, hypervolemia, and hemodynamic instability.

Evaluated Parameters

The parameters recorded and evaluated included ensuring bacterial eradication, presence of septic shock, clinical response (C-reactive protein, procalcitonin and leukocyte counts, positive end-expiratory pressure, fraction of inspired oxygen, sputum characteristics), colistin dose (mg/d), duration of colistin use (day), the dose and duration of additional antibiotics used if necessary, total duration of MV (day), percutaneous dilatation tracheostomy (PDT) performed during the patient's hospital stay in the ICU, if PDT was performed, on



Flowchart for the Study According to CONSORT 2010 Flow Diagram

which day of hospitalization (day), total length of stay in the ICU (day), need for RRT, and eventual discharge or mortality.

The primary endpoint of the study was RRT requirement according to the KDIGO criteria for colistin-dependent AKI used in patients with AcB-related VAE, while the secondary endpoint of the study was differences in mortality and discharge rates between patients who underwent RRT and those who did not.

Statistical Analysis

The mean, standard deviation, median lowest, median highest, frequency, and ratio values were used in the descriptive statistics of the data. The distribution of variables was measured using the Kolmogorov–Smirnov test. The unpaired sample t-test and Mann–Whitney U test were used to analyze quantitative independent data. The paired sample t-test and Wilcoxon test were used to analyze the dependent quantitative data. The chi-square test was used in the analysis of qualitative independent data, whereas Fisher's exact test was used when the conditions of the chi-square test were not met. The SPSS program (version 26.0) was used in the analyses.

RESULTS

Electronic and written files of 2662 patients were examined. There were 85 (3.19%) registered VAEs. Screening results revealed that AcB-related VAEs were detected in 28 patients (32.9%, 28/85). The demographic data of the patients are presented in Table 1. The most common reasons for hospitalization in the ICU were respiratory failure, diabetes mellitus (DM), and DM-related complications. The types and frequencies of antibiotics combined with colistin used for the treatment of AcB-related VAEs are shown in Table 2. While bacterial eradication was achieved in 14 (50%) patients, 22 (78.6%) had symptoms of septic shock. Clinical response to colistin treatment was obtained in 14 (50%) patients, the mean colistin dose was 298.2 ± 85.5 mg/d, and the mean period of colistin use was 14.3 ± 8.6 days. The mean duration of MV was 38.7 ± 28.4 days,

Table 1. Patient Demographics

	Min to Max	Median	Mean ± SD	n (%)
Age, y	18.0 to 93.0	64.5	57.1 ± 23.5	
Gender				
Female				10 (35.7)
Male				18 (64.3)
BMI, kg/m^2	18.0 - 32.0	26.0	25.9 ± 3.1	
APACHE II Score	12.0 - 40.0	28.5	27.5 ± 7.3	
ICU Admission Diagnosis				
Respiratory Failure				9 (32.1)
Sepsis				3 (10.7)
DM and Related Complications				9 (32.1)
Cerebrovascular Disease				5 (17.9)
Post-resuscitation Care				6 (21.4)
Hepatic Failure				2 (7.1)
Acute Ischemic Heart Disease				2 (7.1)
Monitorization After Surgery				3 (10.7)
Eclampsia				1 (3.6)
Polytrauma				8 (28.6)
Heart Failure				3 (10.7)

Abbreviations: BMI, body mass index; APACHE, acute physiology and chronic health evaluation; ICU, intensive care unit; DM, diabetes mellitus.

Table 2. Antibiotics Combined with Colistin in the Treatment of *Acinetobacter Baumannii*-related Ventilator-associated Pneumonia

Combination Ratio of Antibiotics with Colistin (%)	
1: Meropenem	96.4
2: Tigecycline	35.7
3: Linezolid	32.1
4: Anidulafungin	25
5: Fluconazole	0.7
6: Ciprofloxacin	7.1
7: Vancomycin	25
8: Imipenem	3.57
9: Ceftazidime	3.57
10: Teicoplanin	3.57
11: Trimethoprim + Sulfamethoxazole	3.57
12: Metronidazole	3.57

and 15 patients (53.6%) required PDT. While the MV period until PDT was 19.7 ± 9.5 days, the duration of ICU hospitalization was found to be 45.9 ± 38.0 days (Table 3).

Eight (28.6%) patients were classified as having stage I, four (14.3%) as having stage II, and eight (28.6%) as having stage III AKI, which was evaluated according to the KDIGO criteria (Table 3). Eight of the 28 patients (28.6%) had KDIGO stage III acute

Table 3. Findings with *AcB*-related VAE and Data on Colimycin Treatment, MV Duration, PDT Requirements and Duration of PDT, ICU Total Length of Stay and AKI Classification According to KDIGO Criteria

	Min to Max	Median	Mean ± SD	n (%)
Bacterial Eradication				
No		14		50.0
Yes		14		50.0
Septic Shock				
No		6		21.4
Yes		22		78.6
Clinical Response				
No		14		50.0
Yes		14		50.0
Colistin Dosage, mg/d	100.0 to 450.0	300.0	298.2 ± 85.5	
Colistin Administration Duration, d	2.0 to 29.0	15.0	14.3 ± 8.6	
Mechanical Ventilation Duration, d	11.0 to 109.0	30.5	38.7 ± 28.4	
PDT				
No		13		46.4
Yes		15		53.6
Mechanical Ventilation Duration Before PDT, d	1.0 to 41.0	18.5	19.7 ± 9.5	
KDIGO Criteria				
Normal		8		28.6
I		8		28.6
II		4		14.3
III		8		28.6
Length of Stay in ICU, d	11.0 to 180.0	33.0	45.9 ± 38.0	

Abbreviations: PDT, percutaneous dilational tracheostomy, KDIGO, kidney disease improving global outcomes; VAE, ventilator associated event; ICU, intensive care unit; AKI, acute kidney injury.

kidney injury and required RRT. There was no difference in age ($P > .05$), sex ($P > .05$) and body mass index ($P > .05$) between patients who needed RRT (Group II) and those who did not (Group I) (Table 4). Acute Physiology and Chronic Health Evaluation II score ($P > .05$), bacterial eradication ($P > .05$), the presence of septic shock ($P > .05$), clinical response to treatment ($P > .05$), daily colistin dose ($P > .05$), the duration of colistin use between the two groups ($P > .05$), the duration of MV ($P > .05$), need for PDT ($P > .05$), and the duration of MV until PDT ($P > .05$) did not differ (Table 5). There was no significant difference between the two groups in terms of length of stay in the ICU ($P > .05$) and mortality ($P > .05$). RRT was more common in post-resuscitation care patients diagnosed on ICU admission ($P < .05$, Table 6).

DISCUSSION

In our nosocomial infection surveillance system, the incidence of VAEs was 3.19% (85/2662). Approximately 2.4 to 14.7% of the cases of pneumonia develop in critically ill patients per thousand ventilator days.[13] According to the European Union data, the incidence of VAEs is around 9%.[14] The decrease in the incidence of VAEs in recent years may be due to the increased experience of hospital infection control teams and the sensitivity of modernized registry systems. However, great efforts have been made to reduce the incidence of VAEs.[15,16] In addition, some risk factors, such as advanced age, respiratory

Table 4. Demographical Differences Between Groups

	Group 1 = RRT (-)		Group 2 = RRT (+)		*P*
	Mean ± SD (n, %)	Median	Mean ± SD (n, %)	Median	
Age, y	569 ± 25.2	62.5	57.6 ± 20.0	66.0	> .05 [m]
Gender					
Female	8 (40)		2 (25)		> .05 [x²]
Male	12 (60)		6 (75)		
BMI, kg/m^2	25.4 ± 2.9	26.0	27.3 ± 3.2	27.0	> .05 [m]

[m]Mann-whitney u test
x²Chi-square test
Abbreviations: RRT, renal replacement therapy; BMI, body mass index.

Table 5. Comparison of APACHE II Scores, Bacterial Eradication, Presence of Septic Shock, Clinical Response to Therapy, Daily Colistin Dose and Administration Duration, MV Duration, PDT Requirement and Days on Ventilation Prior to PDT Between Groups

	Group 1 = RRT (-)		Group 2 = RRT (+)		*P*
	Mean ± SD (n, %)	Median	Mean ± SD (n, %)	Median	
APACHE II Score	27.3 ± 7.2	27.5	28.3 ± 7.9	28.5	> .05 [m]
Bacterial Eradication					
No	10 (50)		4 (50)		> .05 [x²]
Yes	10 (50)		4 (50)		
Septic Shock					
No	5 (25)		1 (12.5)		> .05 [x²]
Yes	15 (75)		7 (87.5)		
Clinical Response					
No	10 (50)		4 (50)		> .05 [x²]
Yes	10 (50)		4 (50)		
Colistin Dosage, mg/d	297.5 ± 89.6	300.0	300.0 ± 80.2	300.0	> .05 [m]
Colistin Administration Duration, d	14.5 ± 8.9	15.0	14.0 ± 8.4	14.0	>.05 [m]
Mechanical Ventilation Duration, d	37.8 ± 27.8	31.0	40.9 ± 31.8	30.5	>.05 [m]
PDT					
No	10 (50)		3 (37.5)		>.05 [x²]
Yes	10 (50)		5 (62.5)		
Days on Ventilator Before PDT, d	18.5 ± 8.7	17.0	22.4 ± 11.6	21.0	>.05 [m]

[m]Mann-Whitney U test
x²Chi-square test
Abbreviations: RRT, renal replacement therapy; APACHE, acute physiology and chronic health evaluation; PDT, percutaneous dilational tracheostomy

Table 6. Mean ICU Admission Duration, ICU Admission Diagnosis, Mortality Differences Between Groups

	Group 1 = RRT (-)		Group 2 = RRT (+)		*P*
	Mean ± SD (n, %)	Median	Mean ± SD (n, %)	Median	
ICU hospitalization period (days)	47.2 ± 40.3	36.5	42.9 ± 33.6	30.5	> .05 [m]
ICU Admission Diagnosis					
Respiratory failure	7 (35)		2 (25)		> .05 [x²]
Sepsis	3 (15)		0 (0)		> .05 [x²]
DM and related complications	7 (35)		2 (25)		> .05 [x²]
Cerebrovascular disease	4 (20)		1 (12.5)		> .05 [x²]
Post-resuscitation care	2 (10)		4 (50)		< .05 [x²]
Hepatic failure	1 (5)		1 (12.5)		> .05 [x²]
Acute ischemic heart disease	1 (5)		1 (12.5)		> .05 [x²]
Monitorization after surgery	2 (10)		1 (12.5)		> .05 [x²]
Eclampsia	1 (5)		0 (0)		> .05 [x²]
Polytrauma	7 (35)		1 (12.5)		> .05 [x²]
Heart failure	3 (15)		0 (0)		> .05 [x²]
Mortality					
No	7 (35)		0 (0)		> .05 [x²]
Yes	13 (65)		8 (100)		

[m]Mann-Whitney U test
x²Chi-square test
Abbreviations: RRT, renal replacement therapy; ICU, intensive care unit; DM, diabetics mellitus.

or cardiovascular system disease, organ failure, burns, trauma, acute respiratory distress syndrome, gastric colonization, sinusitis, and aspiration of high gastric residual volume, which affect the development of VAEs, may be present at the time of ICU admission.[17,18] Another reason for the lower VAE incidence may be microorganisms that cannot be produced. While microbiological diagnosis results for VAE were approximately 60 to 80% in the literature[19,20] bacterial eradication was 50% in our study, and our samples were generally taken proximal part of the tracheobronchial tree, not the distal.[21] Our AcB-related VAE rate accounted for 32.9% of all VAEs. We administered combined antibiotic therapy with colistin to all patients.

The most important side effect of colistin use for treating nosocomial infections associated with AcB is nephrotoxicity.[22] The rate of developing nephrotoxicity in patients using colistin was reported to be 6 to 55%, and our results were similar.[23] AKI ratio was 71.4% during colistin treatment of the patients in a recent study. Risk factors for developing nephrotoxicity include advanced age, use of other nephrotoxic drugs together with colistin, and the duration and dose of colistin use.[24,25] The average age of these patients who fitted the KDIGO I-II-II staging was 64.5 years and was not advanced. The average duration of colistin use was 15 days, and the average dose was 300 mg/day. We did not discontinue colistin therapy in our patients to complete treatment. RRT was initiated by adjusting the dose according to daily glomerular filtration rates. Glomeruli are intact in colistin-induced nephrotoxicity, and the side effect is dose-dependent and reversible.[26] Therefore, it is important to maintain this strategy. In studies showing low risk and incidence of nephrotoxicity, AKI definitions were differentiated, and reduced colistin dose regimens were used.[27,28] Combination of some drugs with colistin is known to increase the rate of nephrotoxicity, such as the use of more than two nephrotoxic drugs by Doshi *et al.*[29] and the use of three nephrotoxic drugs by Pogue *et al.*[30] Diuretics, angiotensin-converting enzyme inhibitors, contrast agents, aminoglycosides, and antimicrobial agents such as amphotericin and rifampicin, calcineurin inhibitors, and vasopressors are considered nephrotoxic agents.[31] In our study, we could not determine the relationship of colistin with nephrotoxicity since we did not make a retrospective analysis of the presence of a second nephrotoxic agent. This is one of the most important limitations of the present study. The reason for the relatively high incidence of nephrotoxicity is the potentiation of nephrotoxicity by other nephrotoxic agents used.

According to the KDIGO criteria, RRT was required in eight out of 20 patients (28.6%) in

the stage I-II-II population. All eight patients died. According to this result, colistin-associated nephrotoxicity requiring RRT is associated with a high mortality rate. All our patients who required RRT with CVVHDF were septic shock patients who required vasopressors. Defining AKI using the KDIGO criteria is more predictive than Risk, Injury, Failure, Loss of kidney function, End-stage kidney disease (RIFLE) criteria, which are widely used to predict in-hospital mortality.[32] Moving to the definitions recommended and agreed on by the KDIGO criteria is more advantageous compared with the RIFLE criteria approved definitions with regards to improving patient outcomes with treatment.[33] Therefore, we used the KDIGO criteria in this retrospective study.

As in our patients, AKI and continuous RRT can cause significant removal of active colistin from the bloodstream with high extracorporeal clearance, thereby reducing antibacterial efficacy.[34] The doses administered may be insufficient. Just as kidney function is monitored in patients using colistin, colistin levels should be monitored in patients receiving continuous RRT. The possibility of colistin absorption in hemofiltration filters may lead to treatment failure.[35]

This study has some limitations. First, it is challenging to generalize the results to different settings and situations resulting from this single-center study. Second, the retrospective design of the study and the surveillance records did not allow us to completely rule out errors between the established relationships. Third, the heterogeneity detected during treatment depended on the decisions of the clinical team and the clinical responses of the patients. Fourth, VAE is not a suitable definition for the clinical situation and management of the patient.[10] Fifth, we did not rule out other agents with nephrotoxic effects. Sixth, we could not obtain records on the day of nephrotoxicity and the day of the treatment period when RRT was started. Finally, because plasma colistin levels could not be measured, we could not explain the relationship between pharmacokinetic, pharmacodynamic, and toxicodynamic studies and nephrotoxicity.

We believe that periodic monitoring of renal function, modification of the colistin dose, avoidance of the use of nephrotoxic agents together with colistin, and shortening the duration of antimicrobial therapy can minimize the nephrotoxic effect potential of this valuable and adept antibiotic. Ultimately, clinicians will always face the dilemma of the possibility of AKI, with the expectation of microbiological and clinical treatment success during colistin therapy. Dose selection should be carefully studied, AKI should be well known, precautions should be taken in time, and effective RRT should be applied without sacrificing the antibacterial activity in high-risk patients with multiple comorbidities who are obese and in need of other nephrotoxic drugs.

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