Evaluation of Acute Renal Failure After Acinetobacter Baumannii-based Ventilator-associated Event: A Retrospective Cohort Study

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Abstract

Background: Ventilator-associated event (VAE) is the major complication caused mechanical ventilation (MV). We aimed to evaluate whether acute renal failure (ARF) has developed in patients who had been followed-up due to diagnosis of VAE with Acinetobacter baumannii (AcB), and whether renal replacement therapy (RRT) was used, and its relationship with mortality in patients who developed colistin during their treatment.

Methods: Retrospective evaluation of the hospital electronic information system records of 2,622 patients were conducted in three years. Patients who had AcB-related VAE and underwent parental colistin treatment were evaluated according to age, gender, diagnosis for intensive care unit (ICU) administration, Acute Physiology and Chronic Health Evaluation (APACHE) II score, colistin dose and treatment duration, requirement for additional antibiotics, total time required for MV, total duration of ICU stay, presence of septic shock, requirement for percutaneous dilatation tracheostomy (PDT), ARF staging according to Kidney Disease Improving Global Outcomes criteria, requirement for RRT and mortality.

Results: Total number of VAE cases was 85 (3.19%). AcB-related VAE was detected in 28 patients (32.9%). Bacterial eradication was achieved in 14 patients (50%), clinical response was received in 14 patients (50%), mean colistin dose was 298.2±85.5 mg/day, mean duration of colistin treatment was 14.3±8.6 days. ARF was detected as Stage-I in eight patients (28.6%), Stage-II in four (14.3%) and Stage-III in eight patients (28.6%). There was no difference between patients in need of RRT and those who did not, in terms of age, gender and body mass index. APACHE II score, bacterial eradication, presence of septic shock, clinical response to therapy, daily dose of colistin, duration of colistin treatment, MV duration, PDT requirement and time were similar in groups receiving RRT or not.

Conclusion: Colistin treatment of AcB-related VAE caused ARF in 71.5% of the patients and led to serious conditions in 25% of patients requiring RRT.

Background

Since the last ten years, because of the limitations of ventilator-associated pneumonia (VAP) surveillance definition, there are three definition tiers within the ventilator-associated event (VAE) algorithm: 1) Ventilator-associated condition (VAC) and 2) Infection-related ventilator-associated complication (IVAC), and 3) Possible VAP (PVAP) (1, 2). The Centers For Disease Control And Prevention (CDC) recommended using this definition, moreover it includes objective criteria for ventilatory-associated lower respiratory tract infections (VA-LRTI) (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 infectious agents. 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 develops in the ICU (5) and the mortality rate is between 30–70% (6).

The increase in the frequency of infections caused by multi-drug resistant gram-negative bacteria, especially Pseudomonas spp. and Acinetobacter spp., and the difficulties in their treatment have brought polymyxins back to the agenda (7). Colistin is one of the drugs in this group and the most important side effect of it 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).

In our study, we aimed to evaluate whether acute renal failure (ARF) developed in patients who were given colistin for the treatment of AcB-related VAE between January 1, 2017 and December 31, 2019 at ICU, and the need for RRT in patients with ARF and mortality rate of the patients.

Methods

Setting and subjects:

This study was carried out after the approval of the local ethics committee of the hospital (date: 15.05.2020, number: 2020.05.1.09.041) between 01.01.2017-31.12.2019. The files and the record of the hospital electronic information system Patients who were treated and followed at the ICU of the Anesthesiology and Reanimation Clinic in a tertiary referral hospital were retrospectively evaluated.

The inclusion criteria were being a patient who were diagnosed with AcB-related VAE according to CDC criteria for VAE (10) and developed ARF while being treated with parenteral colistin according to Kidney Disease Improving Global Outcomes (KDIGO) criteria (11) at the ICU (Figure 1). Patients who were younger than 18 years, who were pregnant, who had previous history ARF, who had chronic renal failure (CRF) and end stage renal disease (ESRD), had intermittent and/or continuous non-invasive mechanical ventilation (NIMV), who had developed pneumonia and/or septic shock and who were treated with colistin via inhalation were excluded from the study.

Microbiological evaluation:

Sputum, endotracheal aspirate (ETA), nonbronchoscopic bronchoalveolar lavage (mini-BAL) or bronchoscopic specimens (bronchoscopic aspirate, BAL) were used for bacteriological culture. For quantitative assessment of lower respiratory tract samples that were 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 (MIU) of colistin is equivalent to approximately 30 mg dose (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 3 ARF, acidosis, electrolyte imbalance, hypervolemia, and hemodynamic instability.

Evaluated parameters:

The parameters recorded and evaluated were ensuring bacterial eradication, presence of septic shock, clinical response (C-Reactive protein (CRP), procalcitonin and leukocyte counts, positive end expiratory pressure (PEEP), FiO_2, sputum characteristics), colistin dose (mg / day), duration of colistin use (day), the dose and duration of use of additional antibiotics used if necessary, total duration of the mechanical ventilation (MV) (day), percutaneous dilatation tracheostomy (PDT) was performed during the patients' hospitalization in the ICU, if PDT was performed, on 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 the RRT requirement according to KDIGO criteria in colistin-dependent ARF 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:

Mean, standard deviation, median lowest, highest, frequency and ratio values were used in the descriptive statistics of the data. The distribution of variables was measured with the Kolmogorov-Smirnov test. Unpaired sample t-test and Mann-Whitney U test were used to analyze quantitative independent data. Paired sample t-test and Wilcoxon test were used in the analysis of dependent quantitative data. Chi-Square test was used in the analysis of qualitative independent data, while Fisher’s Exact test was used when the conditions of Chi-Square test were not met. SPSS 26.0 program was used in the analyzes.

Results

Electronic and written files of a total of 2662 patients were examined. The number of registered VAE cases was 85 (3.19%). Screening results revealed that AcB-related VAE was detected in 28 patients (32.9%; 28/85). The demographic data of the patients are given in Table 1. The most common reasons for hospitalization in the ICU were respiratory failure and diabetes mellitus (DM) and DM-related complications. The types and frequencies of antibiotics combined with colistin in the treatment of AcB-related VAE are shown in Table 2. While bacterial eradication was achieved in 14 (50%) of the patients, 22 (78.6%) had symptoms of septic shock. While clinical response to colistin treatment was obtained in 14 (50%) patients, the mean colistin dose was 298.2 ± 85.5 mg / day and the mean period of colistin use was 14.3 ± 8.6 days. While the mean duration of MV was 38.7 ± 28.4 days, 15 of the 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%) of the patients were classified as Stage-I, four (14.3%) as Stage-II, and eight (28.6%) as Stage-III when the ARF was evaluated according to the KDIGO Criteria (Table 3). Eight of 28 patients (28.6%) had KDIGO Stage-III AKI and needed RRT. There was no difference in age (p = 0.939), gender (p = 0.454) and BMI (p = 0.183) between patients who needed RRT (Group II) and those who did not (Group I) (Table 4). APACHE II scoring (p = 0.750), bacterial eradication (p = 1.000), presence of septic shock (p = 0.640), clinical response to treatment (p = 1.000), daily colistin dose (p = 0.974) and duration of colistin use between both groups (p = 0.899), the duration of MV (p = 0.899), the need for PDT (p = 0.549), and the duration of MV until PDT (p = 0.609) did not differ (Table 5). There was no difference between the two groups in terms of length of stay in the ICU (p = 0.6290) and mortality (p = 0.053). RRT was more common in post-resuscitation care patients diagnosed with ICU admission (p = 0.038; Table 6).

Discussion

In our nosocomial infection surveillance system, the incidence of VAE was found to be 3.19% (85/2662). Approximately in 2.4-14.7% cases of pneumonia develop in critically ill patients per thousand ventilator days (13). According to European Union data, the incidence of VAE is around 9% (14). The decrease in the incidence of VAE 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 VAE (15, 16). In addition, some of these risk factors such as advanced age, respiratory or cardiovascular system disease, organ failure, burns, trauma, acute respiratory distress syndrome (ARDS), gastric colonization, sinusitis, aspiration of high gastric residual volume, which affect the development of VAE, may be present in the admission of patients to the ICU (17, 18). Another reason why we have less VAE incidence may be microorganisms that we cannot produce. While microbiological diagnosis results for VAE were around 60-80% in the literature (19, 20), bacterial eradication was 50% in our study, and our samples were generally taken from the proximal of the tracheobronchial tree, not the distal (21). Our AcB-related VAE rate was 32.9% of all VAE. We applied combined antibiotic therapy with colistin in all these patients.

The most important side effect of colistin use in the treatment of nosocomial infections associated with AcB is nephrotoxicity (22). The rate of developing nephrotoxicity in patients using colistin was reported to be 6-55% and our results were similar (23). ARF ratio was 71.4% during colistin treatment of the patients in a recent study. Risk factors for developing nephrotoxicity are 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 fit the KDIGO I-II-II staging was 64.5 years and is not advanced. The duration of colistin use was 15 days on average and the average dose was 300 mg / day. We did not discontinue colistin therapy in any of our patients with the effort of completing the treatments. We started RRT in its indication by adjusting the dose according to daily glomerular filtration rate values. Glomeruli are intact in colistin-induced nephrotoxicity, and the side effect is dose-dependent and reversible (26). Therefore, this fact was important for us to maintain this strategy. In studies showing low risk and incidence of nephrotoxicity, ARF 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 use of more than two nephrotoxic drugs by Doshi et al. (29) and use of three nephrotoxic drugs by Pogue et al. (30) . Diuretics, angiotensin-converting enzyme inhibitors, contrast agents, aminoglycosides, antimicrobial agents such as amphotericin and rifampicin, calcineurin

inhibitors and vasopressors are considered nephrotoxic agents (31). In our study, we could not determine the relation of colistin with nephrotoxicity since we did not make a retrospective analysis of the presence of a second nephrotoxic agent. This drawback is one of the most important limitations of our study. The reason behind the relatively high incidence of nephrotoxicity is the potentiation of nephrotoxicity by other nephrotoxic agents we use.

According to the KDIGO criteria, RRT was required in eight of 20 patients (8/20, 28.6%) in the Stage I-II-II population. All of these 8 patients were mortal. According to this result, colistin-associated nephrotoxicity requiring RRT has a high mortality. All of our patients who needed RRT with CVVHDF were septic shock patients who needed vasopressors. Defining ARF by 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 KDIGO criteria is more advantageous compared to RIFLE definitions with regards to improving patient outcomes with treatment (33). For this reason, in this retrospective study, we used monitoring with KDIGO criteria in order to be both more up-to-date and more guiding.

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

We had some limitations in this study. First, it is the difficulty of generalizing the results to different settings and situations resulting from being a single center study. Second, the retrospective design of the study and the surveillance records did not allow us to completely exclude errors between established relationships. The third was the heterogeneity detected during treatment depending on the decisions of the clinical team and the clinical response of the patients. The forth was that the VAE is not suitable definition for clinical situation and management of the patient (10). The fifth was that we do not exclude other agents with nephrotoxicity effects and cannot connect with our results. The sixth was that we could not reach the records on the day of nephrotoxicity and the day of the treatment period when RRT was started. And, finally, since plasma colistin levels could not be measured, we could not explain the relationship between pharmacokinetic, pharmacodynamic and toxicodynamic studies and nephrotoxicity.

Conclusion

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

Abbreviations

AcB: Acinetobacter baumannii

ARF: Acute renal failure

CDC: The Centers For Disease Control And Prevention

CRF: Chronic renal failure

CRP: C-Reactive protein

CVVHDF: Continuous venovenous hemodiafiltration

DM: diabetes mellitus

ESRD: End stage renal disease

ETA: Endotracheal aspirate

ICU: Intensive care unit

IVAC: Infection-related ventilator-associated complication

KDIGO: Kidney Disease Improving Global Outcomes

Mini-BAL: Nonbronchoscopic bronchoalveolar lavage

MIU: One million international units

MV: Mechanical ventilation

NIMV: Non-invasive mechanical ventilation

PDT: Percutaneous dilatation tracheostomy

PEEP: Positive end expiratory pressure

PVAP: Possible ventilator-associated pneumonia

RIFLE: Risk, Injury, Failure, Loss of kidney function, End-stage kidney disease

RRT: Renal Replacement Therapy

VAC: Ventilator-associated condition

VAE: Ventilator-associated event

VA-LRTI: Ventilatory-associated lower respiratory tract infections

VAP: Ventilator-associated pneumonia

Declarations

Acknowledgement

Not applicable.

Declarations

All authors of the manuscript have read and agreed to its content and are accountable for all aspects of the accuracy and integrity of the manuscript in accordance with ICMJE criteria.

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All methods were performed in accordance with the relevant guidelines and regulations by including a statement.

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Ethics approval and consent to participate

This study was carried out after the approval of the Ethics Committee of Istanbul Bagcilar Training and Research Hospital (date: 15.05.2020, number: 2020.05.1.09.041).

Informed consent of the all participants were obtained.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable. We do not want to share our data sets during review prior the publication because of scientific plagiarism. Even so, we are ready to present the data sets when you want. The data sets used and/or analysed during the current study available from the corresponding author on reasonable request.

Competing interest

The authors declare they have no competing interests.

Authors' contributions

Conception: FTA, SD, FGO

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Data Collection and/or Processing: FTA, FGO, SD

Analysis and/or Interpretation: KE, SD, MSS

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Tables

Table 1. Patient demographics

		Min-Max	Median	Mean±SD/n-%
Age (year)		18.0 - 93.0	64.5	57.1 ± 23.5
Gender	Female			10 35.7%
	Male			18 64.3%
BMI (kg/m²)		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%

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%

Table 3. Findings with AcB-associated VAE and data on colimycin treatment, MV duration, PDT requirements and duration of PDT, ICU total length of stay and ARF classification according to KDIGO criteria

		Min-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/day)		100.0	-	450.0	300.0	298.2	±	85.5
Colistin adminisration duration (days)		2.0	-	29.0	15.0	14.3	±	8.6
Mechanical ventilation duration (day)		11.0	-	109.0	30.5	38.7	±	28.4
PDT	No					13		46.4%
	Yes					15		53.6%
Mechanical ventilation duration before PDT (day)		1.0	-	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 (day)		11.0	-	80.0	33.0	45.9	±	38.0

PDT: Percutaneous dilational tracheostomy, KDIGO: Kidney Disease Improving Global Outcomes, VAE: Ventilator associated event, ICU: Intensive care unit, ARF: Acute renal failure

Table 4. Demographical differences between groups

		Group 1=RRT (-)				Group 2=RRT (+)				p	
		Mean±SD (n-%)			Median	Mean±SD (n-%)			Median		
Age (years)		569	±	25.2	62.5	57.6	±	20.0	66.0	0.939	m
Gender	Female	8		40.0%		2		25.0%		0.454	X^2
	Male	12		60.0%		6		75.0%			
BMI (kg/m²)		25.4	±	2.9	26.0	27.3	±	3.2	27.0	0.183	m

m: Mann-Whitney U test / X^2 Chi-square test

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	0.750	m
Bacterial Eradication	No	10		50.0%		4		50.0%		1.000	X^2
	Yes	10		50.0%		4		50.0%			
Septic shock	No	5		25.0%		1		12.5%		0.640	X^2
	Yes	15		75.0%		7		87.5%			
Clinical response	No	10		50.0%		4		50.0%		1.000	X^2
	Yes	10		50.0%		4		50.0%			
Colistin dosage (mg/day)		297.5	±	89.6	300.0	300.0	±	80.2	300.0	0.974	m
Colistin adminisration duration (day)		14.5	±	8.9	15.0	14.0	±	8.4	14.0	0.899	m
Mechanical ventilation duration (day)		37.8	±	27.8	31.0	40.9	±	31.8	30.5	0.899	m
PDT	No	10		50.0%		3		37.5%		0.549	X^2
	Yes	10		50.0%		5		62.5%			
Days on ventilator before PDT (day)		18.5	±	8.7	17.0	22.4	±	11.6	21.0	0.609	m

m: Mann-Whitney U test/ X^2 Chi-square test

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	0.629	m
ICU Admission Diagnosis									
Respiratory failure		7	35.0%		2	25.0%		0.609	X^2
Sepsis		3	15.0%		0	0.0%		0.536	X^2
DM and related complications		7	35.0%		2	25.0%		0.609	X^2
Cerebrovascular disease		4	20.0%		1	12.5%		1.000	X^2
Post-resuscitation care		2	10.0%		4	50.0%		***0.038***	X^2
Hepatic failure		1	5.0%		1	12.5%		0.497	X^2
Acute ischemic heart disease		1	5.0%		1	12.5%		0.497	X^2
Monitorization after surgery		2	10.0%		1	12.5%		1.000	X^2
Eclampsia		1	5.0%		0	0.0%		1.000	X^2
Polytrauma		7	35.0%		1	12.5%		0.234	X^2
Heart failure		3	15.0%		0	0.0%		0.536	X^2
Mortality	No	7	35.0%		0	0.0%		0.053	X^2
	Yes	13	65.0%		8	100.0%			

m: Mann-Whitney U test/ X^2 Chi-square test

RRT: Renal replacement therapy, ICU: Intensive care unit, DM: Diabetis mellitus

Figures

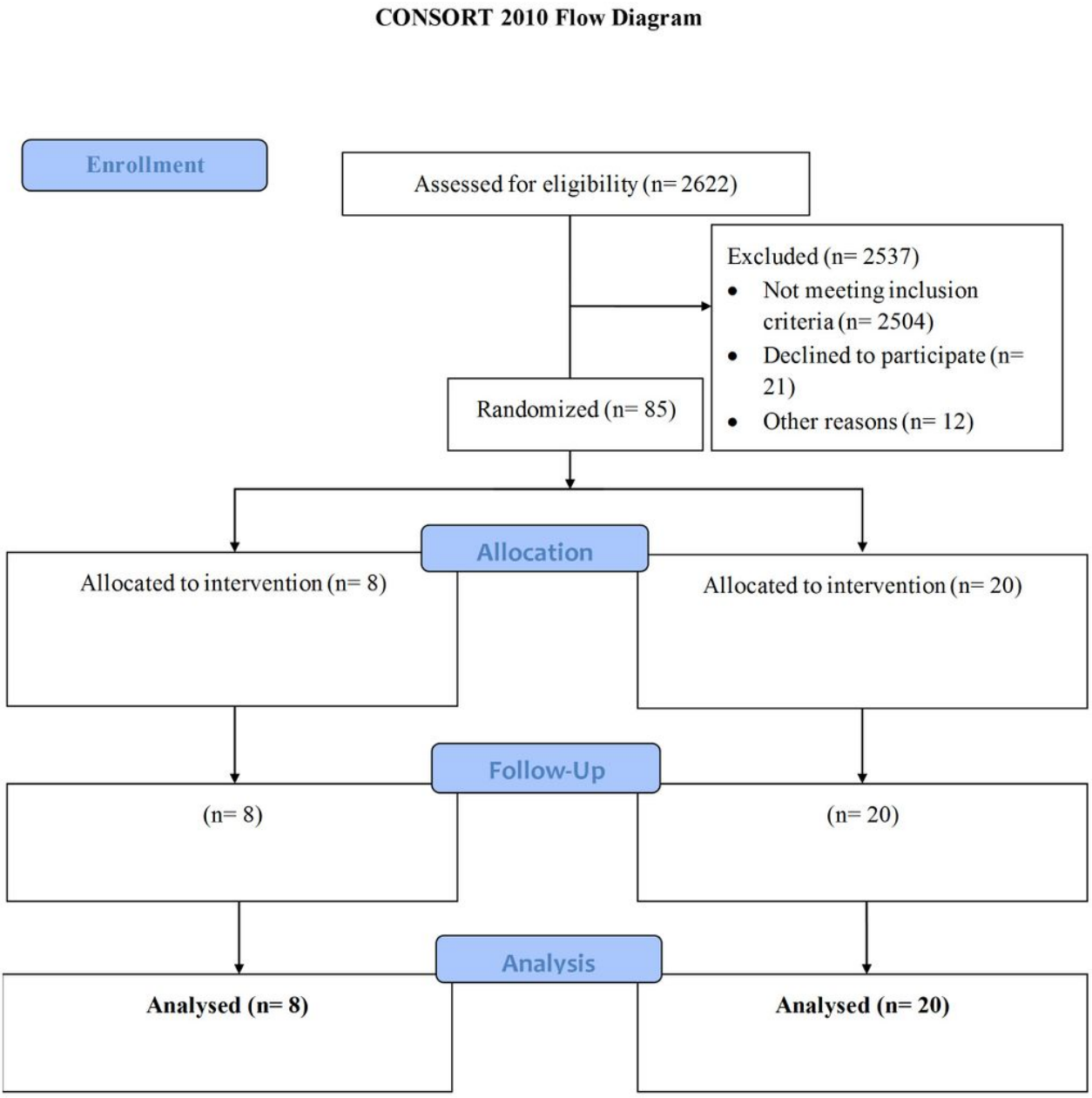

Figure 1

The inclusion criteria were being a patient who were diagnosed with AcB-related VAE according to CDC criteria for VAE (10) and developed ARF while being treated with parenteral colistin according to Kidney Disease Improving Global Outcomes (KDIGO) criteria (11) at the ICU (Figure 1).