ORIGINAL ARTICLE

Impact of the initiation time of colistin treatment for *Acinetobacter* infections

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Abstract This study aimed to address the relationship between the timing of colistin therapy and the outcome, defined as all-cause mortality in the intensive care unit (ICU). A retrospective study was undertaken in a 16-bed ICU of a 750-bed tertiary care hospital. A total of 46 patients who had been administered intravenous colistin treatment for colistin-susceptible-only *Acinetobacter* infections were included in the study. Colistin treatment was initiated in 26 (56.5 %) patients within 24 h of the diagnosis (early administration of colistin), whereas the rest of the patients had obtained delayed treatment (delayed administration of colistin). Of the 46 patients, 21 (45.6 %) died. With univariate analysis, age, age greater than 65 years, APACHE II score more than 20 at baseline, and delayed administration of colistin were found to be significant ($p < 0.05$). Logistic regression analysis revealed a significant association between delayed administration of colistin [adjusted odds ratio (OR), 5.06; confidence interval (CI), 1.18–21.67], and adverse outcome. Other variables included in the final model were underlying disease (OR, 2.81; CI, 1.15–6.84) and APACHE II score at baseline >20 (OR, 3.81; CI, 0.77–18.75). This study found that delayed administration of colistin and underlying disease were independently associated with adverse outcome.

Keywords Intensive care unit · Outcome · Ventilator-associated pneumonia · *Acinetobacter* · Colistin

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Introduction

Acinetobacter is an emerging pathogen in the intensive care unit (ICU) setting causing ventilator-associated pneumonia (VAP) [1]. Carbapenems and sulbactam are effective against most isolates. However, recent increase in carbapenem resistance, mostly caused by the dissemination of OXA carbapenemases, has limited therapeutic options [2–4]. Colistin, which was once eliminated from the market because of its high toxicity, has been found to be effective against carbapenem-resistant *Acinetobacter* and was reintroduced to the market [5, 6]. Parallel to the increasing occurrence of carbapenem-resistant *Acinetobacter* infections, colistin is becoming the mainstay of antimicrobial treatment in ICUs.

After its reintroduction in medical practice, studies focused on the side effects of colistin, particularly on its renal toxicity. Recent studies have reported 10–27 % nephrotoxicity among patients with initially normal renal functions and 58 % among patients having abnormal baseline renal functions with intravenous colistin treatment [6, 7]. Therefore, concern about the toxicity of colistin is still current, and physicians tend to retain this antibiotic until the microbiological confirmation of colistin-susceptible only-*Acinetobacter* (ColsA) infections [8]. Resistance data cannot become available immediately, and therefore during the course of infections caused by ColsA a mean

delay of 96 h in the institution of adequate antibiotic treatment is reported [9]. It is not documented, however, if patients are under serious risk as a result of the delay in the initiation of colistin.

This study investigated whether the timing of administration of colistin significantly affects patient outcome. To our knowledge, there are no published data on the relationship between administration time of colistin and outcome.

Materials and methods

Study design

To asses the impact of timing of initial colistin treatment on survival among patients with ColsA infections, a retrospective study was applied in the ICU of a 750-bed tertiary care hospital. The ICU was a mixed surgical and medical ICU composed of 16 beds.

Patients treated with colistin because they had a nosocomial infection caused by ColsA from September 2010 to March 2012 were eligible. Patients who had been administered colistin but were not confirmed as having ColsA infections were excluded.

This study was approved by the Institute Review Board of Istanbul Medeniyet University, Goztepe Research and Training Hospital (#21/A, 17 April 2012).

Data collection and definitions

Data for the cohort were collected from the ICU records, which were coded primarily by intensive care physicians and by infectious disease physicians during daily visits to the ICU. Variables that were thought to be potentially relevant in terms of outcome were entered in a spreadsheet. These variables were age, gender, ward upon admission to the hospital; underlying disease, which was coded according to the classification of McCabe and Jackson [10]; APACHE II score upon admission to the ICU; APACHE II score at the time of the initiation of colistin; and duration of ICU stay, mechanical ventilation, and duration of colistin treatment.

The endpoint of the study was all-cause mortality in the ICU

According to the McCabe and Jackson classification, patients were categorized as 0, no underlying disease; 1, nonfatal underlying disease; 2, ultimately fatal underlying disease (expected to be fatal in 4 years); and 3, rapidly fatal disease.

In this ICU, infectious disease specialists occasionally administered colistin empirically within 24 h of the clinical

diagnosis of a nosocomial infection. This treatment decision occurred when the infectious disease physician suspected a ColsA infection based on epidemiological observations, some sort of causality, or personal choice. Otherwise, in routine practice of infectious disease consultations in this ICU, colistin i.v. was administered after the confirmation of a ColsA infection at the recommended dosage regimen, which is 3×4.5 million IU days in our unit. Administration of colistin within 24 h of the clinical diagnosis of a nosocomial infection was coded as early administered colistin (EAC); administration of colistin more than 1 day after the clinical diagnosis was coded as delayed administered colistin (DAC). The 24-h cutoff point was selected based on previous studies [11–13]. Both EAC and DAC patients received colistin at the same daily dosage.

Renal side effects of colistin were evaluated according to the RIFLE classification system [14]. This system uses three severity categories (risk, injury, and failure) and two outcome categories (complete loss of kidney function and end-stage kidney disease).

Basically, nosocomial infections were diagnosed according to CDC definitions. VAP was diagnosed in patients having abnormal chest radiography and two or more of the three criteria: (1) purulent tracheobronchial secretion, (2) fever >38.3 °C, and (3) leukocytosis [15].

During the study period, in the microbiology laboratory, bacteria were identified by the API 20NE system (bioMérieux, L'Etoile, France); antimicrobial resistance of isolates were studied by disk diffusion test and interpreted according to the criteria suggested by the CLSI [16, 17].

Statistical comparisons

For statistical comparisons, Stata 12 (StataCorp LP, USA) was used. Continuous variables were compared either by the Student t test or, where required, by unequal variances t test with Welch's approximation. Dichotomous variables were compared by Pearson's χ^2 test or, where required, by Fisher's exact test. Comparisons were always two sided, and significance was evaluated at the 0.05 level.

To explore the significant predictors of adverse outcome for two endpoints, logistic regression analysis was applied. After testing for collinearity, variables were entered and eliminated from the model in a one-by-one backward-selection approach while testing model fit with Hosmer–Lemeshow goodness-of-fit statistics. Continuous variables, such as age and APACHE II score, were tested either as continuous (age, APACHE II score, respectively) or as dichotomous (>65 years, >20 APACHE II score, respectively). Adjusted odds ratios (adj. OR) were obtained from the final model.

To asses the differences between cumulative failure data of early versus late administration of colistin on all-cause mortality in the ICU, Kaplan–Meier failure curves were generated, whereas equality of survivor functions were estimated by log-rank test. Time elapsed between the colistin institution and ICU stay were entered as the survival time data.

Results

During the study period, i.v. colistin was administered to 53 patients for ICU infections, of which 46 were eligible for the study. Of the excluded 7 patients, 4 were eventually confirmed as having *Pseudomonas aeruginosa* infections, whereas 3 did not obtain a microbiological diagnosis. We did not detect polymicrobial infection during the study period.

In the ColsA infection cohort, 2 patients had central nervous system infections, 1 had a soft tissue infection, and 1 had a urinary tract infection. All other patients were diagnosed as VAP. A total of 16 patients diagnosed as VAP were positive for blood cultures along with positive endotracheal cultures. The mean age of the cohort was 52.5 ± 19.5 years; 31 (67 %) patients were men. The mean number of hospitalization days of the cohort in the ICU was 49.7 ± 38.2 days; the mean mechanical days on ventilation was 38 ± 27.6 days; and the mean number of days on colistin was 13 ± 5.8 days. The mean APACHE II score upon admission to the ICU was 15.9 ± 12.1.

Of the 46 patients, 21 (45.6 %) died. Outcome characteristics of patients are presented in Table 1. Briefly, with univariate analysis, age, age greater than 65 years, APACHE II score greater than 20 at baseline, and DAC were significant with $p < 0.05$. Having an underlying disease was at borderline significance with $p = 0.051$.

Duration of the ICU stay was significantly longer among survivors, as expected. However, because this variable is not a risk factor but a consequence of the outcome, it is not included in the logistic regression model. All patients in this ICU received mechanical ventilation because only patients who required mechanical ventilation were accepted. Duration of mechanical ventilation and duration of colistin treatment did not differ among the groups. In addition, exposure to an expanded-spectrum antibiotic before the administration of colistin was not significantly associated with the outcome.

We did not detect a neurological side effect associated with colistin treatment. According to the RIFLE classification, acute kidney injury did not develop among 24 (54.35 %) patients during colistin treatment. Among the rest, 7 (15.22 %), 12 (26.1 %), and 2 (4.35 %) patients developed kidney injury assigned to risk, injury, and failure

Table 1 Characteristics of patients according to outcome

Variables[a]	Died (n = 21)	Survived (n = 25)	p
Age (years)	58.8 ± 20.9	47.2 ± 16.9	0.048
Age >65 (years)	11 (52.4)	5 (20.0)	0.022
Male sex	14 (66.7)	17 (68.0)	0.923
Ward			0.626
Emergency department	13 (61.9)	16 (64.0)	
Surgery department	1 (4.8)	3 (12.0)	
Internal medicine department	4 (19.1)	5 (20.0)	
Other hospital	3 (14.3)	1 (4.0)	
ICU days	37.3 ± 22.1	60.2 ± 45.7	0.033
MV days	34.1 ± 22.4	41.3 ± 31.5	0.373
Colistin days	12.9 ± 6.4	13.2 ± 5.5	0.886
APACHE II score			
At ICU admission	16.8 ± 10.8	15.3 ± 13.3	0.670
Baseline	17.7 ± 11.2	14.5 ± 8.2	0.284
Baseline >20	9 (42.9)	4 (16.0)	0.044
Underlying disease			0.051
None	5 (23.8)	13 (52.0)	
Not fatal	8 (38.1)	10 (40.0)	
Ultimately fatal	5 (23.8)	2 (8.0)	
Rapidly fatal	3 (14.3)	0 (0.0)	
Prior AB	13 (61.9)	18 (72.0)	0.467
Bacteremia	7 (33.3)	9 (36.0)	0.85
DAC	13 (61.9)	7 (28.0)	0.021

Values are presented as *n* (% column) or mean (±SD)

[a] Ward, the department or ward from which the patient was referred to the intensive care unit (ICU); ICU days, number of days in ICU; MV days, number of days with mechanical ventilation; colistin days, number of days colistin administered; APACHE II score, at baseline is the score recorded at the time of infection diagnosed; underlying disease, according to McCabe and Jackson classification (explained in the text); prior AB, exposure to an expanded-spectrum antibiotic before the administration of colistin; DAC, delayed administration of colistin

categories, respectively. Renal complications were almost similar and so were not statistically significant among EAC and DAC groups.

Following the univariate comparisons, a regression model was built in a backward-selection approach. Initially, age, gender, ward, APACHE score, underlying disease, bacteremia, and DAC were included in the model. In each iteration one variable was excluded from the model, depending on the likelihood-ratio tests and the model fit statistics. Age was tested as continuous or dichotomous (>65 years) variables separately. APACHE II scores were tested in three forms: first was the initial score recorded upon admission to the ICU, second was the baseline score at the time of infection diagnosis, and third was a

Table 2 Variables in the final logistic regression model and adjusted odds ratios (OR) with 95 % confidence intervals (CI)

	OR (95 % CI)
DAC[a]	5.06 (1.18–21.67)
Underlying disease	2.81 (1.15–6.84)
APACHE II baseline >20	3.81 (0.77–18.75)
Age >65 (years)	2.58 (0.51–13.02)[b]
ICU days	0.98 (0.95–1.02)

[a] DAC, delayed administration of colistin; underlying disease and APACHE II >20, are as in Table 1

[b] Age >65 and ICU days were excluded in the final step
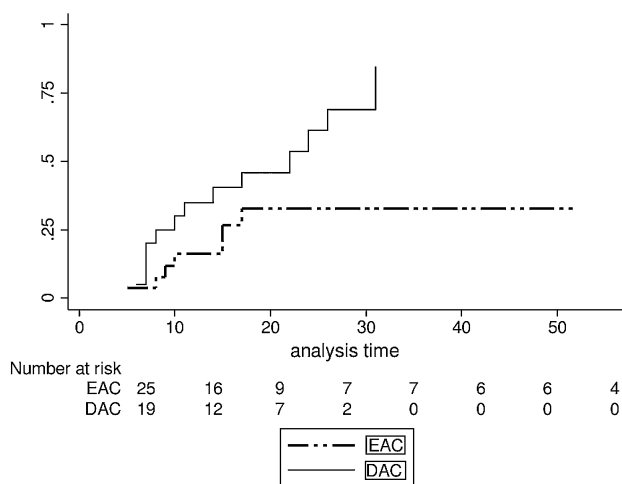
Fig. 1 Kaplan–Meier cumulative mortality (failure) curves of delayed administered colistin group (*DAC*) versus early administered colistin group (*EAC*). Log-rank test for equality of survivor functions was 0.032. The risk table, presented below the figure, shows the number of at-risk patients at 7-day intervals

dichotomous variable (baseline >20). The final model included colistin initiation time "DAC," "underlying disease," and "APACHE II score >20 at baseline" (Table 2). Among these, DAC and underlying disease were significant as independent predictors of the outcome. The adjusted OR for DAC was 5.06 (CIs, 1.18–21.67) and for underlying disease was 2.81 (1.15–6.84). We repeated the final model by restricting patients to those with a diagnosis of VAP (42 patients). In this subgroup, the significance of DAC (adj. OR, 4.6; CI, 1.04–20.29) and underlying disease (adj. OR, 2.5; CI, 1.04–5.99) did not change.

Survival was apparently better among the EAC according to the log-rank test of survivor functions. Kaplan–Meier failure curves for 8 weeks (56 days) are presented in Fig. 1. In the DAC group maximum ICU stay was 31 days, whereas in the EAC group seven patients survived more than 31 days. Among these, only one died on day 76 and the other six patients survived (maximum, 137 days)

until discharge from the ICU. Of notice was that the cumulative failure (death) was consistency high in the DAC group.

Discussion

Ventilator-associated pneumonia is one of the most complicated infections in the ICU setting in terms of both diagnosis and treatment. The diagnosis of VAP should rely on the existence of microbiological plus clinical and radiographic evidence [15, 18]. However, the performance of diagnostic criteria is poor and can lead to diagnostic errors. Overdiagnosis causes inappropriate use of antibiotics, leading to an increase in the resistance problem. On the other hand, a delay in the initiation of adequate treatment may be harmful [11, 12, 19]. The dilemma between overdiagnosis and early institution of adequate treatment for VAP is even more complicated as a consequence of the increased resistance among nosocomial pathogens.

Recent emergence of ColsA, particularly in ICUs, is of concern. Colistin is the only available treatment option for these infections, and accumulating data are encouraging the use of colistin [20]. In medical practice, however, because of concerns about side effects, colistin is not administered empirically, which causes a delay in the initiation of adequate antibiotic treatment. In one study, Reina et al. [9] showed that delay in the initiation of adequate treatment is more frequent (100 %) among the group who eventually treated with colistin. However, it is not clear if the delay in initiation of colistin is harmful.

A recent study found an association between colistin treatment and adverse outcome [21]. In this study 80 % of patients in both arms, colistin and comparators, received adequate treatment after 24 h of diagnosis. The authors had not performed stratified comparisons including as subgroups those who received adequate treatment before 24 h. In contrast, there are a number of studies in the literature showing that colistin treatment is not inferior to comparators despite being used as a salvage therapy. One of these studies, published by Kallel et al. [8], showed that a favorable response of 76.9 % among multiple drug-resistant *Acinetobacter*- or *Pseudomonas*-infected patients was obtained, although 66.7 % of these had delayed administration of colistin. Similarly, Reina et al. [9] showed that efficacy of colistin is not inferior to that of comparators despite being administered late in the infection course. Finally, a meta-regression analysis documented that the clinical efficacy of colistin is comparable to standard treatment regimens irrespective of its application protocols [20]. However, neither of these studies addressed the influence of timing of colistin administration on outcome.

In our institute, we administer i.v. colistin at a daily dosage of 4.5 million IU three times a day, which is higher than the dosage used in early studies. We decided to increase the daily dosage of colistin because of increasing concerns in recent studies addressing the pharmacokinetics of colistin [22]. These studies demonstrated that when administering 2 million IU colistin three times per day an adequate concentration of free drug could not be achieved in the lung. However, it is not clear if this is the result of the high tissue-binding capacity of colistin [23]. On the other hand, we did not prefer nebulized colistin in our institute, mostly because application of this form is not convenient under our conditions.

Although there are limitations in our study, such as small patient number and data from a single center, results suggest the existence of a significant association between delayed administration of colistin and adverse outcome. Therefore, in centers where ColsA prevalence is high, colistin must be considered in the empirical protocols. However, before making such a critical decision, the question when should we include colistin in the empirical protocols has to be addressed. One study discussed this issue and suggested that including colistin in empirical treatment regimens is feasible if ColsA infections are close to 50 % in an ICU [24] The cut of value for this decision is highly important because the most striking consequence of locating colistin in empirical protocols will be its overusage, which will induce resistance, already a significant concern [25–27]. To address these questions, more studies are required.

As a final word, our study suggests that initiation time of i.v. colistin treatment is significant and that in institutions where ColsA infections are high, colistin has to be considered in empirical protocols.

Conflict of interest None.

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