

Clinical outcomes and nephrotoxicity of colistin loading dose for treatment of extensively drug-resistant *Acinetobacter baumannii* in cancer patients

Wasan Katip¹
Suriyon Uitrakul²
Peninnah Oberdorfer³

¹Department of Pharmaceutical Care, Faculty of Pharmacy, Chiang Mai University, Chiang Mai, Thailand;

²Northern Institute for Cancer Research, Newcastle University, Newcastle upon Tyne, UK; ³Division of Infectious Diseases, Department of Pediatrics, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand

Background: Colistin is a last-line defense therapy against extensively drug-resistant *Acinetobacter baumannii* (XDR-AB). Despite a loading dose of colistin being applied in many clinical practices, studies evaluating the effect of the loading dose of colistin in cancer patients remain limited.

Patients and methods: A retrospective cohort study of cancer patients who received either a loading or non-loading dose of colistin for treatment of XDR-AB was conducted. For each group, the clinical response, bacteriological eradication and serum creatinine were recorded. Logistic regression was applied to evaluate the effects of therapy on each of the three aforementioned outcomes.

Results: One hundred and two patients diagnosed with XDR-AB infections between January 2012 and December 2015 were recruited. Only 75 patients were given a loading dose of colistin. There was no significant clinical and microbiological response in patients in the loading dose group or patients in the non-loading dose group. However, 38 (50.67%) patients in the loading dose group and 6 (22.22%) patients in the non-loading dose group developed nephrotoxicity according to the RIFLE criteria ($p = 0.013$). Multivariate logistic regression analysis showed that independent predictors of clinical response were Charlson score ≥ 4 and duration of colistin treatment ≥ 10 days. Septic shock correlated with both poor clinical and microbiological response. Independent predictors for nephrotoxicity were loading dose colistin and patient's age ≥ 60 years.

Conclusion: Administration of colistin loading dose did not significantly increase clinical response, microbiological response or mortality rate compared to non-loading dose in cancer patients with XDR-AB-related infections. However, nephrotoxicity was significantly higher when patients received loading dose colistin.

Keywords: loading dose, colistin, cancer patients, extensively drug-resistant *Acinetobacter baumannii*, nephrotoxicity, clinical outcome

Introduction

Acinetobacter baumannii is one of serious nosocomial pathogens worldwide, particularly among severely ill patients including cancer patients and those receiving hematopoietic stem cell transplantation.¹ *A. baumannii* infections can be fatal in patients with suboptimal immune defenses, especially cancer patients.¹⁻³ Patients with solid tumors who are infected with *A. baumannii* have the mortality rate of 14.5%.⁴ For patients with both hematologic malignancies and *A. baumannii* infections, the mortality rate increased to 83%.⁵

Colistimethate sodium (CMS) was shown to be highly effective for treating extensively drug-resistant *A. baumannii* (XDR-AB) infections that were usually susceptible

Correspondence: Wasan Katip
Department of Pharmaceutical Care,
Faculty of Pharmacy, Chiang Mai
University, Chiang Mai 50200, Thailand
Tel +66 5394 4334
Fax +66 5322 2741
Email wasankatip@gmail.com

only to colistin.⁶ Pharmacokinetic modeling demonstrated that patients with *A. baumannii* infections who received a loading dose colistin had drug concentration within therapeutic range. Despite a loading dose of colistin was applied in many clinical practices, studies evaluating loading dose colistin in cancer patients remain limited. Furthermore, only a few studies described the outcomes of treating XDR-AB infections with colistin in cancer patients and they were all limited by small sample sizes.⁷⁻⁹

The primary objectives of this study were to determine the clinical response, microbiological response, and nephrotoxicity of administering a loading dose of colistin for treating XDR-AB-related infections in cancer patients. The secondary outcome was the overall mortality rate of cancer patients infected with XDR-AB.

Patients and methods

This retrospective cohort study was performed in cancer patients infected with *A. baumannii* who were admitted to Chiang Mai University Hospital, Chiang Mai, Thailand from January 2012 to December 2015.

The Ethics Committee on Human Research of the Faculty of Medicine, Chiang Mai University approved this study with a waiver of informed consent for retrospective data collection under the condition of anonymously stored data collected. We selected cancer patients with XDR-AB infections from medical chart records and the microbiology laboratory database. Infections were defined according to the Center for Disease Control and Prevention criteria.¹⁰ Patients were included if they were 18 years or older, received colistin for more than 48 hours to treat the documented XDR-AB infection and received only one course of colistin treatment. Patients were excluded if they had other types of gram-negative infections or received hemodialysis or renal replacement therapy. Baseline characteristics included age, sex, intensive care unit (ICU) admission during infection, Charlson score and serum creatinine. The recruited cancer patients with XDR-AB infections were divided into two groups. The loading dose group included patients who received a loading dose of colistin (9 million IU of CMS; 300 mg colistin base activity [CBA]) once at the start of treatment course and then regular dose (4.5 MIU; 150 mg CBA) infused for 1 hour in every 12 hours. Patients in the other group received regular dose (150 mg CBA) every 12 hours since the start of treatment. Colistin dose was also adjusted in patients with renal impairment. In patients with moderate-to-severe renal impairment (creatinine clearance rate <50 mL/min), the dose and dosing interval were adjusted according to Cockcroft and Gault creatinine

clearance estimates: maintenance dose of 150 mg CBA every 24 hours for creatinine clearance rate of 20–50 mL/min or 150 mg CBA every 48 hours for creatinine clearance rate of <20 mL/min was administered. The duration of colistin for each of patients depends on type of infection.

Antimicrobial susceptibility tests were performed according to the guidelines of the Clinical and Laboratory Standards Institute (CLSI) (formerly the National Committee for Clinical Laboratory Standards); E-test was used to determine susceptibility of *A. baumannii*.¹¹ XDR-AB was defined as resistance to penicillins, cephalosporins, fluoroquinolones, aminoglycosides and carbapenems (colistin sensitive only).^{2,3}

Outcome assessment

The clinical response of colistin was assessed by resolution or partial resolution of fever, leukocytosis and local signs and symptoms of XDR-AB-related infections at the end of treatment. Clinical failure was defined as failure to meet all criteria for clinical response. Microbiological response was defined as obtaining two consecutive negative XDR-AB cultures from the site of infection after the initial positive culture, whereas microbiologic failure was defined as persistence of the original causative organism in the subsequent specimen cultures. Nephrotoxicity was counted if patients developed any grades of renal failure based on RIFLE criteria. The RIFLE criteria contain three grades of acute renal failure (risk, injury and failure) and two long-term outcomes (loss and end-stage renal disease).¹²

Statistical analysis

Statistical analysis was performed using Stata software, version 14 (Stata-Corp, College Station, TX, USA). All variables were compared between the loading and non-loading dose groups. Mean with standard deviation and median with interquartile range were used for continuous data, while frequency and percentages were used to describe nominal data. Fisher's exact test was used to compare categorical variables. Continuous variables were compared by independent *t*-tests if they had normal distribution and Wilcoxon rank sum tests if the data had non-normal distribution. All statistical tests were considered two sided, and statistical significance was defined as $p \leq 0.05$.

Logistic regression analysis was used to determine the effects of colistin on three primary outcomes: clinical response, microbiological response and nephrotoxicity. All variables with $p < 0.25$ by univariate analysis were further investigated by multivariate logistic regression analysis. In addition, all variables that demonstrated a trend toward

association with outcomes were forced into the model at the discretion of the investigators, and statistical significance was set at $p \leq 0.05$.

Results

During the study period, 102 patients met the inclusion criteria; 75 had been treated with a loading dose of colistin and 27 had been treated with non-loading dose of colistin. Most patients were females (loading dose group, 62%; non-loading

dose group, 59%; $p = 1.000$) (Table 1). The mean age in the loading dose group (59.89 ± 14.46) was not significantly different from the non-loading dose group (65.18 ± 11.81) ($p = 0.091$).

Type of patients' malignant tumors was similar between the loading dose and non-loading dose groups. Other baseline characteristics such as ICU status, septic shock incidence, total CMS dose and duration were similar between the two groups.

Table 1 Demographic and clinical characteristics of patients in the loading dose and non-loading dose groups

Characteristic	Loading dose (n = 75)	Non-loading dose (n = 27)	p-value
Sex (no. [%] of patients)			
Male	29 (38)	11 (41)	1.000
Female	46 (62)	16 (59)	
Age (years), mean \pm SD	59.89 \pm 14.46	65.18 \pm 11.81	0.091
Type of malignancy, n (%)			0.741
Solid	66 (88)	23 (85)	
– Lung cancer	17 (22.67)	5 (18.52)	
– Brain cancer	6 (8.00)	2 (7.41)	
– Liver and bile duct cancer	9 (12.00)	5 (18.52)	
– Urogenital cancer	6 (8.00)	4 (14.81)	
– Colon cancer	8 (10.67)	2 (7.41)	
– Bone cancer	5 (6.67)	2 (7.41)	
– Head and neck cancer	8 (10.67)	1 (3.70)	
– Gynecologic cancer	7 (9.33)	2 (7.41)	
Hematologic	9 (12)	4 (15)	
– Lymphoma	4 (5.33)	4 (15)	
– Leukemia	5 (6.67)	0 (0)	
ICU status, n (%)	41 (54.67)	18 (66.67)	0.365
Septic shock, n (%)	39 (52.00)	19 (70.37)	0.117
Charlson score, mean \pm SD	4.10 \pm 2.34	4.44 \pm 2.45	0.527
Baseline SCr, mg/dl, median (IQR)	0.7 (0.5–1.1)	0.8 (0.6–3)	0.036
SCr increase from baseline, median (IQR)	0.8 (0.2–1.7)	0.1 (0–1.6)	0.031
Baseline GFR, ml/min, median (IQR)	100.09 (60.1–117.8)	75.2 (21.41–110.9)	0.019
Lowest GFR after colistin treatment, ml/min, median (IQR)	34.4 (16–88.9)	28.13 (11.6–79.6)	0.453
Total CMS dose, g, median (min–max)	2.25 (4.95–10.35)	1.95 (0.3–7.5)	0.2984
Type of nephrotoxic medications,* n (%)			
Aminoglycosides	5 (6.76)	2 (7.41)	1.000
Diuretics	54 (72)	21 (78)	0.621
Amphotericin B	6 (8)	1 (3.7)	0.672
Vasopressor	43 (58.11)	19 (70.37)	0.356
Vancomycin	40 (53.33)	15 (55.56)	1.000
Duration of IV colistin (days), mean \pm SD	9.56 \pm 5.18	11.14 \pm 5.90	0.192
Length of hospital stay, days, mean \pm SD	43.93 \pm 32.26	44.29 \pm 28.55	0.959
Source of infection			0.318
Pneumonia	53 (70.67)	16 (59.26)	
Bacteremia	5 (6.67)	1 (3.70)	
UTI	12 (16.00)	5 (18.52)	
Other	5 (6.67)	5 (18.52)	
Colistin MICs, median (min–max)	0.25 (0.094–1.5)	0.25 (0.064–1.5)	0.898

Notes: *One patient can have >1 drugs. Other represents inter costal drainage, pus from wound.

Abbreviations: SD, standard deviation; ICU, intensive care unit; SCr, serum creatinine; IQR, interquartile range; GFR, glomerular filtration rate; MIC, minimum inhibitory concentration; CMS, colistimethate sodium; IV, intravenous; UTI, urinary tract infection

Outcomes

Only nephrotoxicity was significantly higher in patients in the loading dose group than those in the non-loading dose group. Other outcomes such as clinical response, microbiological response and overall mortality did not show significant difference between the two groups, although the clinical and microbiological response trended in favor of the loading dose group (Table 2).

Univariate and multivariate logistic regression analysis of the outcomes

Univariate analysis and multivariate logistic regression analysis (Table 3) showed that patients treated with colistin for more than 10 days demonstrated good clinical response, while Charlson score ≥ 4 was related to poor clinical response in patients with XDR-AB infection. Moreover, septic shock was related to poor clinical and microbiological responses (Table 3). Finally, loading dose colistin was associated with nephrotoxicity.

Table 2 Overall outcomes and toxicity in loading dose and non-loading dose groups

Outcome	Loading dose (n = 75)	Non-loading dose (n = 27)	p-value
Clinical response	40 (53.33)	13 (48.15)	0.661
Microbiological response	55 (73.33)	15 (55.56)	0.097
Nephrotoxicity	38 (50.67)	6 (22.22)	0.013

Note: Bold indicates data is significant ($p < 0.05$).

Table 3 Univariate and multivariate logistic regression analysis of independent factors associated with outcomes in cancer patients treated with colistin for XDR-AB (n=102)

Outcome and variable	Crude OR	95% CI	p-value	Adjusted OR	95% CI	p-value
Clinical response						
Loading dose colistin	1.23	0.51–2.97	0.644	1.03	0.38–2.75	0.948
Age ≥ 60 years	0.77	0.35–1.69	0.519	1.13	0.46–2.80	0.780
Septic shock	0.30	0.13–0.70	0.005	0.26	0.10–0.64	0.004
Baseline SCr ≥ 1 mg/dl	0.61	0.26–1.43	0.263	0.68	0.26–1.77	0.437
Charlson score ≥ 4	0.82	0.69–0.98	0.029	0.40	0.16–0.98	0.047
Duration of colistin ≥ 10 day	1.04	0.43–2.46	0.929	2.83	1.17–6.81	0.020
Microbiological response						
Loading dose colistin	2.2	0.88–5.49	0.091	2.27	0.84–6.13	0.105
Age ≥ 60 years	0.81	0.35–1.89	0.631	1.09	0.42–2.80	0.850
Septic shock	0.31	0.12–0.79	0.015	0.28	0.10–0.78	0.015
Baseline SCr ≥ 1 mg/dl	1.00	0.41–2.48	0.02	1.30	0.47–3.53	0.606
Charlson score ≥ 4	0.92	0.39–2.15	0.844	0.93	0.37–2.33	0.882
Duration of colistin ≥ 10 days	2.22	1.00–4.91	0.048	2.49	0.98–6.32	0.054
Nephrotoxicity						
Loading dose colistin	2.59	1.05–6.40	0.039	5.80	1.45–23.25	0.013
Age ≥ 60 years	2.05	0.89–4.67	0.088	3.28	1.09–9.87	0.034
Use vasopressor drug	1.57	0.68–3.63	0.287	1.76	0.63–4.90	0.278
Baseline SCr ≥ 1 mg/dl	0.58	0.24–1.39	0.229	0.60	0.20–1.86	0.385
Duration of colistin ≥ 10 days	1.11	0.44–2.75	0.820	0.58	0.22–1.53	0.274

Abbreviations: XDR-AB, extensively drug-resistant *Acinetobacter baumannii*; OR, odds ratio; CI, confidence interval; SCr, serum creatinine.

Note: Bold indicates data is significant ($p < 0.05$).

Discussion

Our study showed that clinical response, microbiological response and overall mortality did not differ significantly between the loading dose and non-loading dose groups. However, nephrotoxicity in the loading dose group was significantly higher than in the non-loading dose group.

Previous studies suggested that 9 MIU colistin followed by maintenance dose of 4.5 MIU every 12 hours was an effective and safe therapy for infections due to multidrug-resistant gram negative pathogens.^{13,14} However, the role of a loading dose of colistin has not been definitively established in cancer patients. Previous studies were conducted in only a small number of patients and colistin was administered in general population without immunocompromised status.^{13,14} The clinical response of loading dose colistin for treating XDR-AB infections in our study was lower than previous studies (53.3% vs. 63–82.1%).^{13,14} This might be because of compromised immunity in cancer patients. However, no difference in clinical response between patients receiving loading dose and non-loading dose was found in our study (53.33% and 48.15%, respectively; $p = 0.661$). Microbiological response also was insignificant different between the two groups (73.33% and 55.56%, respectively; $p = 0.097$), although loading dose colistin showed better response. Similarly, a recent retrospective study by Nazer et al⁷ reported 66.2% microbiological response in cancer patients infected with carbapenem-resistant *A. baumannii* (CRAB) who were treated with high-dose colistin.⁷

When adjusting the potential confounders by multivariate logistic regression analysis, loading dose colistin was neither associated with clinical response (odds ratio [OR], 1.03; 95% confidence interval [CI], 0.38–2.75) nor microbiological response (OR, 2.27; 95% CI, 0.84–6.13) compared with non-loading dose colistin. These results were not significantly different, perhaps because the minimal inhibitory concentration in our study was low (0.064–1.5) in both groups. These results were supported by Álvarez-Marín et al¹⁵ who showed that non-loading dose of colistin was effective for treating CRAB ventilator-associated pneumonia caused by strains with high susceptibility to colistin.¹⁵

Focusing on nephrotoxicity, loading dose colistin significantly increased incidence of nephrotoxicity compared to non-loading (50.67% and 22.22%, respectively; $p = 0.013$). These results were similar to the study by Nazer et al,⁷ which reported >60% nephrotoxicity rate when high-dose colistin (9 MIU per day, divided into three doses) was used for treating cancer patients infected with CRAB.⁷

Furthermore, loading dose of colistin was found to be an independent risk factor for nephrotoxicity after adjusting potential confounders (OR, 5.80; 95% CI, 1.45–23.25) and so high-dose colistin should be used with caution in patients with impaired renal function. Pogue et al¹⁶ found that nephrotoxicity occurred in patients who received high dose more than those who received low dose of colistin. Their study also showed that nephrotoxicity was dose dependent. The other factor that had correlation with nephrotoxicity in our study was age equal or greater than 60 years (OR, 3.28; 95% CI, 1.09–9.87).

In addition, a correlation was found between long duration of colistin treatment (≥ 10 days) and clinical response. On the other hand, patients with septic shock or Charlson score ≥ 4 tended to have poor clinical response. Also, septic shock was a risk factor for poor microbiological response. The study likewise suggested that if critically ill cancer patients suffered from AB infection, then they would have poor outcomes.¹⁷

Our study has several limitations. This was a retrospective study and so it might contain inherent bias and incompleteness in data collection. Further study therefore should be performed prospectively to confirm these results and determine the optimal dose of colistin for XDR-AB treatment. In addition, our study did not measure serum concentration of colistin because it was not measured routinely in the hospital. Sample size could be considered as a limitation in our study as well. Nevertheless, to the best of our knowledge, our study is the first and largest-to-date to compare loading

dose with non-loading dose of colistin in the treatment of cancer patients with XDR-AB-related infections.

In conclusion, loading dose colistin did not affect clinical response, microbiological response and mortality rate in cancer patients with XDR-AB-related infections but significantly increased nephrotoxicity rate. Loading dose colistin therefore should be given carefully in elderly patients or patients with renal impairment and avoided in patients infected with highly colistin-sensitive *A. baumannii*. In addition, if patients with Charlson score ≥ 4 or septic shock, poor clinical and microbiological responses should be taken into account and properly managed.

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Disclosure

The authors report no conflicts of interest in this work.

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