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Original Article

Adjunctive therapy of intravenous colistin to intravenous tigecycline for adult patients with non-bacteremic post-surgical intra-abdominal infection due to carbapenem-resistant *Acinetobacter baumannii*☆

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ABSTRACT

Post-surgical intra-abdominal infections (IAIs) due to carbapenem-resistant *Acinetobacter baumannii* (CRAB) are difficult to treat due to suboptimal peritoneal penetrations of several antimicrobial agents. Tigecycline has favorable outcomes of treating IAIs due to multidrug-resistant organisms but occurrence of breakthrough bacteremia has been observed because this agent has low serum level. Colistin has *in vitro* activity against CRAB but data on treatment of IAIs is limited due to poor peritoneal penetration. The purpose of this retrospective study is to explore the outcomes of adjunctive intravenous (IV) colistin to IV tigecycline in the treatment of IAIs caused by CRAB. Of 28 patients with non-bacteremic post-surgical IAIs due to CRAB, 14 patients received IV tigecycline alone and 14 patients received IV tigecycline with IV colistin. The 14-day, 30-day, in-hospital mortality rates, the rate of breakthrough bacteremia and the rate of bacterial eradication were not significantly different. The adjunctive therapy of IV colistin was associated with significantly higher rates of renal complications (10/14) than those receiving IV tigecycline alone (3/14) (P value = 0.023). In addition, the patients receiving adjunctive IV colistin had significantly more unfavorable non-clinical outcomes including longer length of hospital stay (P value = 0.049) and higher antimicrobial cost (P value = 0.008) and non-antimicrobial costs (P value = 0.037). In this study, adjunctive IV colistin to conventional IV tigecycline in the treatment of non-bacteremic post-surgical IAIs caused by CRAB did not yield clinical benefit but caused higher renal complication and unfavorable non-clinical outcomes.

1. Introduction

Infection due to carbapenem-resistant *Acinetobacter baumannii* (CRAB) is one of the most important nosocomial problems, causing unfavorable clinical outcomes and high economic burden [1]. Antimicrobial options for this infection are extremely constrained due to multidrug resistance (MDR) of this organism and primarily include colistin and tigecycline [2]. Furthermore, these active antimicrobial agents have their own limitations. For example, the serum concentration of tigecycline is typically below the organism's minimum inhibitory concentrations while colistin poorly penetrates infected tissues and has significant toxicities [3,4]. From the clinical standpoint, whether these *in vitro* active agents, either alone or in combination, confer beneficial outcomes remains unclear in certain infection types, intra-abdominal infections (IAIs) being one of them [5,6].

Post-surgical IAIs are one type of nosocomial infections that are difficult to treat due to suboptimal peritoneal penetrations of

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several antimicrobial agents particularly initial dosage of colistin and aminoglycosides when administered intravenously [4,7,8], risk of secondary bacteremia associated with additionally poor outcomes [9,10], and increased risk of involvement of MDR organisms due to empiric or prophylactic strategies of antimicrobial agent use for abdominal surgery [11,12].

Tigecycline, a glycylcycline derived from tetracycline, was designed to overcome several mechanisms underlying tetracycline resistance and is approved for use in the treatment of IAIs [3]. Although several reports showed favorable outcomes of treating IAIs due to MDR organisms with tigecycline, clinical failure especially occurrence of breakthrough bacteremia has been observed [13]. The organisms causing secondary bacteremia vary but most of them are primary causative organisms of IAIs including CRAB [9,10]. Colistin, a polypeptide agent of the polymyxin class, also has *in vitro* activity against CRAB [4]. Clinical efficacy data of colistin in the treatment of IAIs due to CRAB are insufficient since it is not typically used as the primary agent due to poor peritoneal penetration, particularly prior to equilibration period [14]. We hypothesized that addition of intravenous colistin to tigecycline may have clinical benefit in the treatment of IAIs caused by CRAB. Here we present a retrospective analysis of IAI cases due to CRAB which were treated with intravenous tigecycline with or without adjunctive intravenous colistin.

2. Materials and methods

2.1. Setting and patients

We retrospectively reviewed the clinical records of adult (age ≥18 years) patients with post-surgical IAIs due to CRAB during the period of January 2012 to December 2017 at Songkhlanagarind Hospital, an 800-inpatient bed tertiary care hospital in Southern Thailand. The diagnosis was made on the basis of presence of at least one of following: core body temperature ≥38 °C or abdominal pain, or evidence of purulent discharge from any intra-abdominal drainage. *A. baumannii* was identified on the basis of standard biochemical reactions and confirmed with polymerase chain reaction (PCR) for the detection of $_{bla}$OXA-51-like genes. The isolates with a positive result for $bla_{\text{OXA-51-like}}$ genes were assigned as *A. baumannii*. For the isolates with a negative result for $bla_{\text{OXA-51-like}}$ genes, *rpoB* gene sequencing was performed and compared to published sequences [15]. Carbapenem susceptibility was tested by the disk diffusion technique, followed by the agar dilution method to determine the minimal inhibitory concentrations (MICs) of imipenem and meropenem. An MIC of ≥16 μg/ml was used as the resistance breakpoint. Tigecycline susceptibility was determined with the disk diffusion method and interpreted using the U.S. Food and Drug Administration (FDA) breakpoint for *Enterobacteriaceae*. Colistin susceptibility testing was performed by the disk diffusion technique and Etest according to the manufacturer's guidelines (AB Biodisk, Sweden). An Etest colistin strip (MIC range, 0.06 to 1024 μg/ml) and broth microdilution were applied to each plate and incubated at 35 °C for 20 h. Susceptibility was defined as having an inhibition zone of ≥11 mm and MIC of ≤2 μg/ml [16].

2.2. Study design

The patients with IAIs due to CRAB with concomitant bacteremia at the onset of infection were excluded from the analysis. The study design was based on the comparisons of outcomes of the 2 groups of patients with post-surgical IAIs with CRAB (group 1; the patients received intravenous [IV] tigecycline without IV colistin, group 2; the patients received IV tigecycline and IV colistin as adjunctive therapy). According to the stewardship policy for tigecycline and colistin, these regimens were initiated only after microbiological confirmation of CRAB was reported. The primary outcome in this study was 30-day mortality rates. The secondary outcomes were 14-day and in-hospital mortality as well as length of hospital stay (LOS) and costs of treatment after infection. Since January 2012, the standard dosing regimens of tigecycline and colistin in this institute are as follows: tigecycline 100 mg for the initial dose, then 50 mg every 12 h and colistin base activity (CBA) 5 mg/kg/dose or 300 mg for the initial dose, then 2.5 mg/kg/dose or 150 mg every 12 h with renal dose adjustment made according to estimated creatinine clearance.

2.3. Data collection

The medical records of the patients were reviewed. Information extracted included age, sex, underlying diseases or comorbidities, and initial Physiology and Chronic Health Evaluation (APACHE) II score, and immunological status. Immunocompromised status was defined as persistent neutropenia (absolute neutrophil count of $<0.5 \times 10^9$ neutrophils/l) or receiving immunosuppressive therapy (cytotoxic agents or chemotherapy within 6 weeks or corticosteroids at a dose equivalent to or higher than 10 mg of prednisolone daily for more than 5 days within 4 weeks prior to the onset of infection). Adequate control of infection source was defined as removal of primary lesion. Adequate drainage was defined as ≥50% decrease in the size of collection after a percutaneous drain was placed or additional surgery was done. Abdominal fluid was collected and cultured within a week after treatment. We obtained abdominal fluid from additional surgery or existing drains until end of treatment or removal of the drain. Bacterial eradication was defined with negative results for bacterial culture. Renal complication was defined according to the RIFLE classification as follows: risk for renal dysfunction (rise of serum creatinine [sCr] by ≥ 1.5 times or decrease in glomerular filtration rate [GFR] ≥25%, or urine output <0.5 ml/kg/hour in 6 h), renal injury (rising of sCr 2 times or decrease in GFR ≥50% or urine output <0.5 ml/kg/hour in 12 h), renal failure (rise of sCr by ≥ 3 times, or decrease in GFR ≥75% or urine output <0.3 ml/kg/hour in 24 h or anuria in 12 h), loss of renal function (complete loss of renal function >4 weeks) and end-stage renal disease (complete loss of renal function >3 months). GFR was determined as creatinine clearance estimated by Cockcroft-Gault Equation with ideal body weight [17]. Hospital costs were divided into antimicrobial pharmacy costs and the remaining costs (non-antimicrobial cost). Only LOS and costs after infection were included into analysis.

2.4. Statistical analysis

Clinical characteristics of the survivors and non-survivors were compared by tabulation, followed by chi-square test or Fisher's exact test as appropriate for categorical variables and Student's *t*-test for continuous variables. The differences of levels of variables were expressed with crude odds ratio (OR) and 95% confidence interval (CI). The sufficient variables and those with *P* values < 0.2 were included in a multivariate logistic regression model. These models were fitted to assess the effect of each characteristic, expressed as adjusted ORs and 95% CIs. The significance level was set at 0.05.

3. Results

Between January 2012 and December 2017, 38 patients were diagnosed with post-surgical IAIs due to CRAB, accounting for 6.5% of those with post-surgical IAIs during this period. Of these, 7 patients with concomitant pathogens were excluded, with extended-

spectrum β-lactamase (ESBL)-producing *Escherichia coli* [2], ESBL-producing *Klebsiella pneumoniae* [1], *Pseudomonas aeruginosa* [1], methicillin-resistant *Staphylococcus aureus* (MRSA) [1], *Enterococcus faecium* [1] and *Candida albicans* [1]. Of 31 patients with post-surgical IAIs caused only by CRAB, 3 patients with concurrent bacteremia due to the following organisms were also excluded: CRAB, ESBL-producing *K. pneumoniae* and MRSA. Of the remaining 28 patients with non-bacteremic post-surgical IAIs due to CRAB, 14 patients received IV tigecycline alone and 14 patients received IV tigecycline with IV colistin as the adjunctive therapy. Demographic data, clinical characteristics and treatment of these 2 groups of patients were comparable (Table 1).

The demographic and clinical factors predictive of 30-day mortality are shown in Table 2. Only APACHE II score and adequate source control/drainage were associated with 30-day mortality. Additional therapy with IV colistin and any carbapenems as well as appropriate empirical antimicrobial agents showed no benefit for 30-day mortality.

The outcomes of the 28 patients with non-bacteremic post-surgical IAIs due to CRAB without concomitant infection are shown in Table 3. The 14-day, 30-day, in-hospital mortality rates and the rate of breakthrough bacteremia among patients receiving IV tigecycline plus IV colistin were nominally lower than among those receiving IV tigecycline alone, but the differences did not reach statistical significance. There were only 8 patients (57%) among the patients receiving IV tigecycline alone and 7 patients (50%) receiving IV tigecycline and IV colistin who had bacterial eradication within 7 days after treatment. However, there was no significant difference in the bacterial eradication rates between the groups. There was no significant difference in the rate of breakthrough bacteremia between these 2 groups. Three patients receiving IV tigecycline plus IV colistin had breakthrough bacteremia due to ESBL-producing *K. pneumoniae* [2] and MRSA [1]. Four patients receiving IV tigecycline alone had breakthrough bacteremia due to ESBL-producing *K. pneumoniae* [2], ESBL-producing *E. coli* [1] and MRSA [1]. All isolates of *K. pneumoniae* and *E. coli* causing breakthrough bacteremia were susceptible to both tigecycline and colistin. Kaplan-Meier survival curves of those receiving IV tigecycline plus IV colistin and receiving IV tigecycline alone are shown in Fig. 1. The survival difference between these groups was not significant.

In a subgroup analysis, among 14 patients infected with *A. baumannii* with MIC of imipenem/meropenem ≥32 μg/ml, the in-hospital mortality rate among patients receiving IV tigecycline plus IV colistin (5/7) was borderline higher than those receiving IV tigecycline alone (2/7) with a *P* value of 0.08. Among 12 patients without adequate source control or drainage, the in-hospital mortality rate among the patients receiving IV tigecycline plus IV colistin (6/7) was higher than those receiving IV tigecycline alone (3/5) but this did not reach statistical significance with a *P* value of 0.37. Among the patients with APACHE II score ≥15, the in-hospital mortality rate among patients receiving IV tigecycline plus IV colistin (5/7) was higher than those receiving IV tigecycline alone (2/5) but it did not reach statistical significance, either, with a *P* value of 0.33.

On the other hand, adjunctive therapy of IV colistin was associated with significantly higher rates of renal complications than those receiving IV tigecycline alone. Among 10 patients who

Table 1
Comparisons of clinical features of the patients with non-bacteremic post-surgical intra-abdominal infection due to CRAB receiving IV tigecycline plus IV colistin and receiving IV tigecycline alone.

Parameters	IV tigecycline plus IV colistin (N = 14) (%)	IV tigecycline alone (N = 14) (%)
Demographic		
Age (yrs), median (IQR)	46 (37,57)	45 (36,56)
Male sex, N (%)	8 (57)	8 (57)
Comorbidities, N (%)	9 (64)	9 (64.3)
Baseline serum creatinine, median (IQR)	1.1 (0.7,1.3)	1.7 (1.3,2.1)[a]
Creatinine clearance (mL/min)	70 (48, 103)	45 (39, 67)[b]
Immunocompromised status, N (%)	1 (7)	1 (7)
Year, N (%)		
2012	3 (21.4)	3 (21.4)
2013	3 (21.4)	3 (21.4)
2014	2 (14.3)	2 (14.3)
2015	2 (14.3)	2 (14.3)
2016	2 (14.3)	2 (14.3)
2017	2 (14.3)	2 (14.3)
Clinical characteristics		
Type of surgery, N (%)		
Trauma	2 (14)	2 (14)
Liver/biliary tract	4 (29)	3 (21)
Stomach/intestine	6 (43)	7 (50)
Obstetrics/gynecology	2 (14)	2 (14)
Emergency indication of admission/surgery, N (%)	10 (71)	10 (71)
Initial admission (not mutually exclusive) to ICU, N (%)	8 (57)	8 (57)
APACHE II score, median (IQR)	15 (13,18)	15 (12,17)
Minimal inhibitory concentration of *A. baumannii* (μg/ml)		
imipenem, median (IQR; range)	32 (32, 64; 16–512)	32 (32, 64; 16–512)
meropenem, median (IQR; range)	32 (32, 64; 16–512)	32 (32, 64; 16–512)
Colistin,[c] median (IQR; range)	0.06 (0.06, 0.50; 0.06–1)	0.06 (0.06, 0.50; 0.06–1)
Tigecycline, median (IQR; range)	0.032 (0.016, 0.25; 0.016–0.75)	0.032 (0.016, 0.50; 0.016–0.75)
Treatment		
Adequate source control, N (%)	7 (50)	9 (64)
Additional surgery	2 (14)	3 (21)
Percutaneous drainage	5 (36)	6 (43)
Appropriate empirical antimicrobial agents, N (%)	2 (14)	4 (29)
Time to initiate tigecycline (adjunctive colistin) (days), median (IQR; range)	3 (3,4; 2–5)	3 (3,4; 2–5)
Adjunctive carbapenems, N (%)	8 (57)	8 (57)
Duration of consolidative intravenous antimicrobial treatment, median (IQR; range)	21 (19,28; 12–45)	22 (18,29; 12–49)

[a] *P*-value = 0.003, [b] *P*-value = 0.004, [c] Broth microdilution techniques.

Table 2
Factors influencing 30-day mortality the patients with non-bacteremic post-surgical intra-abdominal infection due to CRAB receiving IV tigecycline plus IV colistin and receiving IV tigecycline alone.

Variables	Values		Crude OR (95% CI)	Adjusted OR (95% CI)	*P*-value[a]
	Survivors (n = 19) (%)	Non-survivors (n = 9) (%)			
Age (years) [median (IQR)]	46 (36,56)	46 (37,57)	1.04 (0.99,1.09)	1.63 (0.43,6.08)	0.470
Male sex	11 (58)	5 (56)	0.91 (0.18,4.50)	1.00 (0.87,6.75)	0.669
Comorbidities	13 (68)	5 (57)	0.58 (0.11,2.95)	1.38 (0.24,7.12)	0.522
Emergency indication for surgery	13 (68)	7 (78)	1.62 (0.26,10.23)	4.99 (0.56,6.54)	0.413
Initial ICU admission	11 (58)	5 (56)	0.91 (0.18,4.50)	1.00 (0.18,2.22)	0.956
APACHE II score [median (IQR)]	15 (13,18)	18 (15,20)	1.69 (1.12,2.50)	1.45 (1.33,2.08)	**< 0.001**
Non-traumatic surgery	17 (89)	7 (78)	0.41 (0.05,3.53)	0.48 (0.11,7.89)	0.507
MIC of meropenem ≥32 μg/ml	10 (53)	6 (67)	1.80 (0.34,9.40)	1.77 (0.78,3.11)	0.235
Appropriate empirical antimicrobial agents	4 (21)	2 (22)	1.07 (0.15,7.31)	1.78 (0.12,4.57)	0.566
Adequate source control/drainage	12 (63)	4 (44)	0.47 (0.09,2.33)	0.89 (0.45,0.95)	**0.039**
Addition of IV carbapenem	12 (63)	4 (44)	0.47 (0.09,2.33)	1.14 (0.11,5.70)	0.683
Addition of IV colistin	10 (53)	4 (44)	0.72 (0.14,3.54)	1.21 (0.14,4.52)	0.563

[a] Multivariate analysis with logistic regression model.

Table 3
Comparisons of outcomes of the patients with non-bacteremic post-surgical intra-abdominal infection due to CRAB receiving IV tigecycline plus IV colistin and receiving IV tigecycline alone.

Outcome	IV tigecycline plus IV colistin (N = 14) (%)	IV tigecycline alone (N = 14) (%)	*P*-value
Clinical outcomes			
Mortality, no. (%) of patients			
14 day	3 (21)	4 (29)	1.000
30 day	4 (29)	5 (36)	1.000
In-hospital	5 (36)	6 (43)	1.000
Renal complication	10 (71)	3 (21)	**0.023**
Risk of renal dysfunction	3 (21)	1 (7)	
Renal injury	4 (29)	2 (18)	
Renal failure	1 (7)	0 (0)	
Loss of renal function	1 (7)	0 (0)	
End-stage renal disease	1 (7)	0 (0)	
Breakthrough bacteremia	3 (21)	4 (29)	1.000
Bacterial eradication within 1 week	7 (50)	8 (57)	0.879
Non-clinical outcomes			
Length of hospital stay after infection (days), median (IQR)	67 (38,70)	40 (16,64)	**0.049**
Length of ventilator-day after infection (days), median (IQR)	3 (1,5)	3 (1,6)	0.987
Length of ICU stay after infection (days), median (IQR)	4 (2,6)	4 (1,7)	0.988
Cost after infection (baht)[a], median (IQR)			
Total hospital	148880 (112398,170688)	103256.5 (78682,110883)	**0.003**
Antimicrobial	67066 (37896,98745)	49224 (19713, 59856)	**0.008**
Non-antimicrobial	69546 (52871,87606)	47360 (37642,63265)	**0.037**

[a] 1 U.S. dollar = 32 baht (as of 31 December 2017).

received adjunctive IV colistin and developed renal complications, 3 patients were diagnosed with renal failure [1], loss of renal function [1] and end-stage renal disease [1], and required renal replacement therapy including intermittent hemodialysis [1] and continuous hemodialysis [2]. The 2 patients who receiving continuous hemodialysis died at day 10 and day 13 after diagnosis of post-surgical IAIs due to CRAB. Of the 8 patients with renal complication who survived, 5 patients had recovery of renal function while 3 patients developed chronic renal disease. Of these 3 patients, one needed long-term hemodialysis. In addition, the patients receiving adjunctive IV colistin had significant unfavorable non-clinical outcomes including longer LOS (*P* value = 0.049) and higher antimicrobial cost (*P* value = 0.008) and non-antimicrobial costs (*P* value = 0.037) (Table 3).

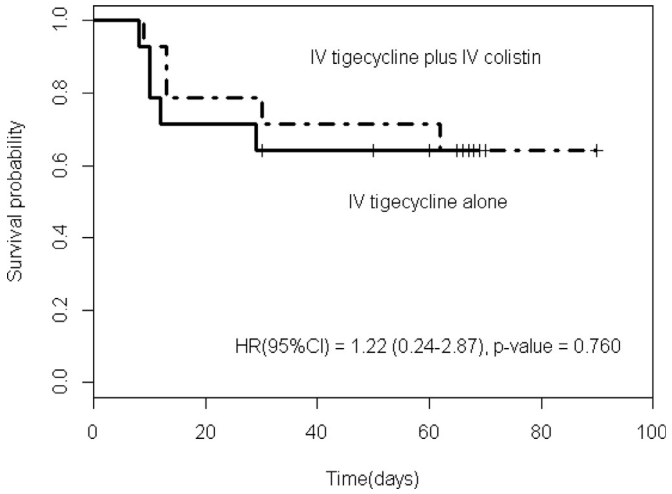

Fig. 1. Kaplan-Meier survival curves of the patients with non-bacteremic post-surgical intra-abdominal infection due to carbapenem-resistant Acinetobacter baumannii; IV: intravenous; HR: Hazard ratio; CI: Confident interval.

4. Discussion

In this study, addition of IV colistin to IV tigecycline for patients with non-bacteremic post-surgical IAIs due to CRAB was not associated with better clinical outcomes including rate of bacterial

eradication, incidence of breakthrough bacteremia, and mortality rates. No benefit on in-hospital mortality was identified among the subgroup of patients without adequate source control/drainage, high APACHE II score or infection with *A. baumannii* with MIC ≥32 μg/ml. Furthermore, addition of IV colistin was associated with higher rate of renal complication and unfavorable non-clinical outcomes including longer LOS, higher antimicrobial and non-antimicrobial costs.

In this study, even though post-surgical IAIs due to CRAB had low incidence, they yielded unfavorable outcomes including substantial mortality, prolonged LOS and high hospital cost. Similar to previous observations, initial severity of illness as well as adequacy of source control and drainage were associated with mortality [18,19]. In contrast with several reports of CRAB infection, appropriateness of empirical antibiotic did not impact mortality. With the policy for control of antimicrobial agent prescription in the institute, no patient received IV colistin/tigecycline as part of their empirical regimens [9,10,12,13]. Also, among few patients receiving active empiric antimicrobial agents, for example aminoglycosides or cefoperazone/sulbactam, the regimens were switched to IV tigecycline and/or IV colistin upon identification of CRAB.

The *in vitro* activity of colistin-containing regimens against CRAB infections has been well established, in combination with active agents for example tigecycline, rifampicin and sulbactam [20]. It is interesting that this study did not show any clinical benefit of adjunctive therapy of IV colistin to IV tigecycline. It is possible that the intra-abdominal levels of colistin were too low to yield clinical benefits [4,14]. Also, with various and unpredictable organisms causing breakthrough bacteremia subsequent to treatment, the benefit of IV colistin to prevent or treat this complication was not observed [9,10]. Thus, among the patients receiving adjunctive intravenous colistin, their creatinine clearances were relatively high, then the probability to achieve appropriate plasma colistin concentration (greater than 1.5 μg/ml) with current loading dose was less than 50% [21]. Finally, all isolates of CRAB in this study were susceptible to tigecycline, which may have been efficacious on its own [22].

This study also underscores the high renal complication rates associated with IV colistin use. The patients in this study frequently developed renal complications despite receiving IV colistin at the recommended doses [23]. The durations of IV colistin in this study were relatively long, and patients with complicated IAIs tend to have volume deficit from third space volume loss, which make them vulnerable to pre-renal renal failure, factors that may account for this observation [24]. Unfavorable non-clinical outcomes including prolonged LOS and high hospital cost among the patients receiving adjunctive IV colistin might at least in part be explained by the need to address renal complications.

There are several limitations in this study to be acknowledged. First, due to the retrospective design, specific reasons for the clinical decision to use additional IV colistin were not available. Though the demographic and clinical characteristics between the patients who received and who did not receive IV colistin were comparable, the possibility of unmeasured confounding factors influencing the survival of the patients remains. Second, due to the small number of the patients in this study, lack of difference of clinical outcomes in either direction might be due to inadequate power of discrimination. With this number in current study, it had only 27% power to detect significant difference in 30-day mortality rates. Third, all CRAB isolates in this study were susceptible to both tigecycline and colistin, thus the findings in this study cannot be generalized to the patients with IAIs due to tigecycline and/or colistin–resistant CRAB. Forth, there were no data on plasma colistin concentrations which could impact on the response of treatment and the likelihood that kidney injury. Last, the highly heterogeneous diagnoses of primary diseases may have influenced the outcomes of IAI patients.

5. Conclusions

This study demonstrated similar clinical outcomes between the patients with non-bacteremic IAIs due to CRAB receiving IV tigecycline alone and addition of IV colistin. However, those receiving adjunctive IV colistin had significantly higher rate of renal complication and unfavorable non-clinical outcomes. With these findings, other options rather than IV colistin for adjunctive therapy to conventional IV tigecycline for the patients with non-bacteremic IAIs due to CRAB should be considered.

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Conflicts of interest

The authors declare that they have no conflict of interest.

Ethical approval

The study protocol was approved by the Institutional Review Board (IRB) of the Faculty of Medicine, Prince of Songkla University (EC: 54-080-14-1-2). The authorized researchers were granted the right to extract the data from the database.

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References

[1] Peleg AY, Seifert H, Paterson DL. *Acinetobacter baumannii*: emergence of a successful pathogen. Clin Microbiol Rev 2008;21:538–82.
[2] Maragakis LL, Perl TM. *Acinetobacter baumannii*: epidemiology, antimicrobial resistance, and treatment options. Clin Infect Dis 2008;46:1254–63.
[3] Stein GE, Babinchak T. Tigecycline: an update. Diagn Microbiol Infect Dis 2003;75:331–6.
[4] Cai Y, Lee W, Kwa AL. Polymyxin B versus colistin: an update. Expert Rev Anti Infect Ther 2015;13:1481–97.
[5] Zusman O, Altunin S, Koppel F, Dishon Benattar Y, Gedik H, Paul M. Polymyxin monotherapy or in combination against carbapenem-resistant bacteria: systematic review and meta-analysis. J Antimicrob Chemother 2017;72:29–39.
[6] Kengkla K, Kongpakwattana K, Saokaew S, Apisarnthanarak A, Chaiyakunapruk N. Comparative efficacy and safety of treatment options for MDR and XDR *Acinetobacter baumannii* infections: a systematic review and network meta-analysis. J Antimicrob Chemother 2018;73:22–32.
[7] Solomkin JS, Mazuski JE, Bradley JS, Rodvold KA, Goldstein EJ, Baron EJ, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clin Infect Dis 2010;50:133–64.
[8] Bailey JA, Virgo KS, DiPiro JT, Nathens AB, Sawyer RG, Mazuski JE. Aminoglycosides for intra-abdominal infection: equal to the challenge? Surg Infect (Larchmt) 2002;3:315–35.
[9] Mansur A, Klee Y, Popov AF, Erlenwein J, Ghadimi M, Beissbarth T, et al. Primary bacteremia is associated with a higher mortality risk compared with pulmonary and intra-abdominal infections in patients with sepsis: a prospective observational cohort study. BMJ open 2015;5:e006616.
[10] Huang J, Ren J, Brakert L, Jiao J, Liu Q, Wang G, et al. A new scoring system to predict blood stream infections in patients with complicated intra-abdominal infections: experience from a tertiary referral hospital in China. Surg Infect (Larchmt) 2018;19:459–66.
[11] Sganga G. New perspectives in antibiotic prophylaxis for intra-abdominal surgery. J Hosp Infect 2002;50(A):S17–21.
[12] Golan Y. Empiric therapy for hospital-acquired, Gram-negative complicated intra-abdominal infection and complicated urinary tract infections: a

systematic literature review of current and emerging treatment options. BMC Infect Dis 2015;15:313.
[13] Bassetti M, McGovern PC, Wenisch C, Meyer RD, Yan JL, Wible M, et al. Clinical response and mortality in tigecycline complicated intra-abdominal infection and complicated skin and soft-tissue infection trials. Int J Antimicrob Agents 2015;46:346–50.
[14] Mimoz O, Petitpas F, Gregoire N, Gobin P, Marchand S, Couet W. Colistin distribution in the peritoneal fluid of a patient with severe peritonitis. Antimicrob Agents Chemother 2012;56:4035–6.
[15] La Scola B, Gundi VA, Khamis A, Raoult D. Sequencing of the *rpoB* gene and flanking spacers for molecular identification of *Acinetobacter species*. J Clin Microbiol 2006;44:827–32.
[16] The european committee on antimicrobial susceptibility testing - EUCAST 2018. 2018. http://www.eucast.org/mic_distributions_and_ecoffs/. [Accessed 25 July 2018].
[17] Kellum JA, Bellomo R, Ronco C. Definition and classification of acute kidney injury. Nephron Clin Pract 2008;109:c182–7.
[18] Montravers P, Lepape A, Dubreuil L, Gauzit R, Pean Y, Benchimol D, et al. Clinical and microbiological profiles of community-acquired and nosocomial intra-abdominal infections: results of the French prospective, observational EBIIA study. J Antimicrob Chemother 2009;63:785–94.
[19] Labricciosa FM, Sartelli M, Abbo LM, Barbadoro P, Ansaloni L, Coccolini F, et al. Epidemiology and risk factors for isolation of multi-drug-resistant organisms in patients with complicated intra-abdominal infections. Surg Infect (Larchmt) 2018;19:264–72.
[20] Song JY, Kee SY, Hwang IS, Seo YB, Jeong HW, Kim WJ, et al. In vitro activities of carbapenem/sulbactam combination, colistin, colistin/rifampicin combination and tigecycline against carbapenem-resistant *Acinetobacter baumannii*. J Antimicrob Chemother 2007;60:317–22.
[21] Nation RL, Garonzik SM, Thamlikitkul V, Giamarellos-Bourboulis EJ, Forrest A, Paterson DL, et al. Dosing guidance for intravenous colistin in critically-ill patients. Clin Infect Dis 2017;64:565–71.
[22] Fan B, Guan J, Wang X, Cong Y. Activity of colistin in combination with meropenem, tigecycline, fosfomycin, fusidic acid, rifampin or sulbactam against extensively drug-resistant *Acinetobacter baumannii* in a murine thigh-infection model. PLoS One 2016;11:e0157757.
[23] Nation RL, Li J, Cars O, Couet W, Dudley MN, Kaye KS, et al. Framework for optimisation of the clinical use of colistin and polymyxin B: the Prato polymyxin consensus. Lancet Infect Dis 2015;15:225–34.
[24] Bratzler DW, Hunt DR. The surgical infection prevention and surgical care improvement projects: national initiatives to improve outcomes for patients having surgery. Clin Infect Dis 2006;43:322–30.