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Factors Associated with Treatment Outcome of Extensively Drug-Resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa* Infection under Colistin Combination Therapy: A Pilot Study

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Background: Healthcare-associated infections (HAI) are among the major concerns worldwide. In Thailand, Gram-negative pathogens have accounted for the major cause of HAI, in particular *Acinetobacter baumannii* and *Pseudomonas aeruginosa* according to epidemiological survey data both local and national levels. Currently, these two pathogenic bacteria are resistant to multiple antimicrobial regimens, including piperacillin/tazobactam, fluoroquinolones, and even carbapenems. Extensively drug-resistant (XDR) Gram-negative bacteria are generally sensitive to colistin but colistin combination therapy (CCT) is advocated to avoid emergence of resistant bacteria. However, the factors associated with treatment outcome in XDR bacterial infection under CCT have not often been addressed.

Objectives: To assess clinical factors associated with treatment outcome under CCT in patients with XDR *A. baumannii* or *P. aeruginosa* infection

Methods: A pilot prospective observational study was conducted between October 2014 and January 2016 in inpatients with XDR *A. baumannii* or *P. aeruginosa* infection receiving CCT. Patients' basic clinical data and maximum plasma colistin level and minimal inhibitory concentration ratios (Cmax/MIC) were collected over a 14-day period.

Results:

- Table 1 demonstrates antibiograms of Ramathibodi Hospital in the years of 2013-2014
- A total of 34 patients were enrolled
- Patients' characteristics and clinical profile associated with microbiological outcome on day 7 of colistin therapy are shown in Table 2
- The average duration of CCT was 10±4 days with 66.67% of patients achieved the target colistin level
- Microbiological success at day 7 of treatment was demonstrated in 15/28 patients
- There was a trend towards higher mortality at day 7 among meropenem–CCT group (3/8 patients)
- All bacteremic and urinary-tract-infection patients had 100% microbiological success while others did not (p-value <0.0001)
- Higher APACHE scores were associated with higher mortality (p-value = 0.031)
- Table 3 shows risk factors for development of AKI in non-dialysis patients undergoing CCT

Table 1. Antibiograms in the years of 2013-2014 of Ramathibodi Hospital, Bangkok, Thailand

	Number of isolates tested	Susceptibility (%)							
Hospital Wide	22,125	TZP	CAZ	IPM	MEM	DOR	CIP	AMK	CST
P. Aeruginosa	1,742	74	75	63	68	72	72	90	100
A.baumannii	1,105	9	10	9	10	9	7	23	100

TZP: piperacillin/tazobactam, CAZ: ceftazidime, IPM: imipenem cilastatin, MEM: meropenem, DOR: doripenem, CIP: ciprofloxacin, AMK: amikacin, CST: colistin

Table 2. Patients' characteristics and clinical profile associated with microbiological outcome on day 7 of colistin therapy

Characteristics	n=28	Microbiol success on day 7 (n=15)	Microbiol failure on day 7 (n=13)	*P*-value
Gender, n (%)				0.885
Female	19	10 (53)	9 (47)	
Age, years	56 ± 20	58 ± 21	54 ± 20	0.598
APACHE II score[a]	22 ± 6	22 ± 6	20 ± 6	0.578
Site, n (%)				0.038
Respiratory tract	18	8 (44)	10 (56)	
Urinary tract	**5**	**5 (100)**	**0 (0)**	
Blood stream	**2**	**2 (13.33)**	**0 (0)**	
Other sites	3	0 (0)	3 (100)	
Partner antibiotic, n (%)				0.654
IPM	**7**	**5 (71)**	**2 (29)**	
CAZ	6	4 (67)	2 (33)	
Tigecycline	6	3 (50)	3 (50)	
MEM	**4**	**2 (50)**	**2 (50)**	
DOR	3	1 (33)	2 (67)	
TZP	1	0 (0)	1 (100)	
Colistin Cmax/MIC >8 (%)	18/27 (67%)	9 (50)	9 (50)	0.785
Colistin Cmin (mg/L)	4.5 ± 3.8	5.8 ± 2.3	3.3 ± 2.2	0.132

*Missing data on 1 patient

Table 3. Risk factors for development of AKI in non-dialysis patients undergoing CCT

Factor	With AKI (n = 19)	Without AKI (n = 10)	*P*-value*
Age (years)	**62 ± 18[a]**	**46 ± 17**	**0.025**
GFR (ml/min/1.73 m²)	**84 ± 33**	**109 ± 25**	**0.030**
Concomitant nephrotoxic agent use[a|c]	9 (47)[b]	6 (60)	0.400
APACHE II score	22 ± 7	20 ± 6	0.504
Colistin Cmax/MIC	16.10 ± 8	14.33 ± 9.49	0.701
Colistin Cmin level (g/L)	5.63±5.77	2.69±2.85	0.083
Length of CCT (days)	11±4	11±4	1.000

[a]Mean ± SD. [b]n (%). [c]Acyclovir, amphotericin B, cisplatin, contrast media, ganciclovir, trimethoprim/sulfamethoxazole, and vancomycin

Conclusions:

- Optimal colistin Cmax/MIC may not be a predictor of CCT success (survival) in treating XDR *A. baumannii* and *P. aeruginosa* infections but APACHE score was.
- Different site of infection benefited from CCT differently.