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Preliminary Study of Colistin versus Colistin plus Fosfomycin for Treatment of Carbapenem-Resistant *Acinetobacter baumannii* Infections

Rujipas Sirijatuphat, Visanu Thamlikitkul

Department of Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand

Ninety-four patients infected with carbapenem-resistant *Acinetobacter baumannii* were randomized to receive colistin alone or colistin plus fosfomycin for 7 to 14 days. The patients who received combination therapy had a significantly more favorable microbiological response and a trend toward more favorable clinical outcomes and lower mortality than those who received colistin alone. (This study has been registered at ClinicalTrials.gov under registration no. NCT01297894.)

Acinetobacter spp. are one of the most common causes of nosocomial pneumonia in Asian countries, including Thailand (1). The overall prevalence of carbapenem resistance in *Acinetobacter* spp. causing nosocomial pneumonia in Thai patients is 82%. The treatment of patients with carbapenem-resistant (CR) *Acinetobacter baumannii* infections at Siriraj Hospital in Bangkok, Thailand, led to the observation that the mortality of the patients who received colistin was 46%, compared with 80% of those who received other antibiotics (2). The observed mortality rate of patients who received colistin alone is still high, even though almost all isolates of CR *A. baumannii* are susceptible to colistin. One of the contributing factors to a modest response to colistin is that monotherapy with colistin may be insufficient. A systematic review on colistin in combination with other antibiotics revealed that colistin plus other antibiotics showed synergy in many isolates of *A. baumannii*, lowered mortality in animals in some studies, and showed no superiority to colistin monotherapy in several small studies in humans (3). Fosfomycin is a broad-spectrum antibiotic that is active against a wide range of Gram-positive and Gram-negative bacteria (4). Fosfomycin has been an alternative drug for the treatment of drug-resistant bacterial infections, especially when combined with other antibiotics, due to its synergistic effect (5, 6). Although the MICs of fosfomycin against clinical isolates of *A. baumannii* in Thailand were rather high (MIC_{50}, 64; MIC_{90}, 128 μg/ml), a combination of 1 μg/ml colistin and 64 μg/ml fosfomycin showed a synergistic effect against two clinical isolates of carbapenem-resistant *A. baumannii* (7).

The objective of this study (ClinicalTrials.gov under registration no. NCT01297894) was to compare the 28-day all-cause mortality, clinical response, and microbiological response of a colistin plus fosfomycin combination with colistin alone for the treatment of CR *A. baumannii* infections.

This was a preliminary open-label randomized controlled study at Siriraj Hospital, which is a 2,300-bed tertiary care university hospital in Bangkok, Thailand, performed from January 2010 to March 2011. The study was approved by the Siriraj Institutional Review Board, and informed consents were obtained from all participating patients. Eligible patients were hospitalized adults age ≥18 years who developed CR *A. baumannii* infection and required treatment with colistin. Carbapenem-resistant *A. baumannii* infection is defined as having clinical signs and symptoms of infection in the presence of CR *A. baumannii* isolated from the relevant clinical specimens. Each patient received colistin according to the decision of the attending physician. Eligible patients were randomized to receive a combination of intravenous colistin (colistimethate sodium) at a dosage of 5 mg of colistin base activity/kg of body weight/day plus intravenous fosfomycin sodium at a dosage of 4 g every 12 h (combination group) or colistin alone at the aforementioned dose (monotherapy group). The duration of treatment was 7 to 14 days, depending on the clinical response and site of infection, except for the patient who died before 7 days and the patient who needed a longer treatment duration, such as for a complicated intra-abdominal infection. Colistin and fosfomycin were given at the same time, and the dosages of both drugs were adjusted according to the renal function of the patients. Each patient was observed daily for clinical assessment until the colistin and fosfomycin therapy for CR *A. baumannii* infection was discontinued or the patient died or left the hospital. Microbiological culture of the specimens taken from the infection site was made on day 3 after starting study treatment and at the end of treatment with colistin and fosfomycin. Renal and liver function tests were performed at least once a week. The clinical outcomes were assessed at 72 h after starting the study treatment, at the end of study treatment, and 28 days after treatment with colistin and fosfomycin. The clinical outcome was classified as favorable outcome (cure or improvement of all attributable signs and symptoms) or nonfavorable outcome (persistence or progression of disease or death). Microbiological responses were classified as eradication (no target organisms found), persistence, or undetermined. Acute kidney injury was defined as at least the injury category (decreasing glomerular filtration rate, >50%, doubling of serum creatinine, or urine production of <0.5 ml/kg/h for 12 h) of the risk, injury, failure, loss of kidney function, and end-stage kidney disease (RIFLE) classification (8).

It was estimated that the 28-day all-cause mortality of CR *A.*

Received 7 November 2013 **Returned for modification** 8 December 2013
Accepted 21 June 2014
Published ahead of print 30 June 2014
Address correspondence to Visanu Thamlikitkul, visanu.tha@mahidol.ac.th.

doi:10.1128/AAC.02435-13

TABLE 1 Characteristics and outcomes of 94 study patients

Patient characteristic with/without carbapenem treatment	Colistin + fosfomycin	Colistin	*P* value
Characteristics of study patients			
n	47	47	
Female (%)	57.4	48.9	0.535
Age (yr)			
Mean ± SD	67.4 ± 17.2	69.2 ± 16.3	0.603
Median (min, max)[a]	69 (31, 96)	73 (30, 97)	
Diabetes mellitus (%)	44.7	23.4	0.050
Cardiovascular disease (%)	17.0	21.3	0.793
Cerebrovascular disease (%)	38.3	14.9	0.020
Chronic kidney disease (%)	14.9	31.9	0.088
Chronic lung disease (%)	21.3	17.0	0.793
Malignancy (%)	36.2	25.5	0.372
Postsurgery (%)	6.4	14.9	0.316
Mechanical ventilator use (%)	83.0	74.5	0.450
APACHE II score at diagnosis			
Mean ± SD	23.0 ± 6.4	21.9 ± 7.9	0.483
Median (min, max)	24 (8, 35)	22 (5, 39)	
Length of hospital stay (days)			
Mean ± SD	46.0 ± 33.4	47.9 ± 53.0	0.429
Median (min, max)	40 (5, 173)	28 (10, 326)	
Prior use of antibiotics within 2 wk (%)	100	95.7	0.495
Type of infection (%)			
Pneumonia	78.7	74.5	0.808
Primary bacteremia	4.3	6.4	1.000
Urinary tract infection	6.4	4.3	1.000
Skin and soft tissue infection	4.3	2.1	1.000
Intra-abdominal or gastrointestinal infection	4.3	8.5	0.677
Central nervous system infection	0	2.1	1.000
Others	2.1	2.1	1.000
Coinfection with (%):			
Klebsiella pneumoniae	4.3	12.8	0.267
Pseudomonas aeruginosa	6.4	2.1	0.617
MRSA[b]	4.3	4.3	1.000
Other organisms[c]	2.1	2.1	1.000
Concurrent antimicrobial agent (%)			
Carbapenem	8.5	17.0	0.354
Piperacillin-tazobactam	2.1	2.1	1.000
Vancomycin	2.1	4.3	1.000
Other antibiotics[d]	4.3	6.4	1.000
Dose of colistin (mean ± SD) (mg/kg)	4.4 ± 1.5	4.0 ± 1.5	0.586
Duration of colistin (days)			
Mean ± SD	10.3 ± 3.9	12.1 ± 8.2	0.521
Median (min, max)	12 (3, 15)	12 (3, 56)	
Duration of fosfomycin (days)			
Mean ± SD	10.0 ± 3.8		
Median (min, max)	12 (3, 14)		
Outcomes of the study patients			
Favorable clinical response (%)			
First 72 h	72.3	66.0	0.655
End of study treatment	59.6	55.3	0.835
28-day all-cause mortality (%)	46.8	57.4	0.409
Infection-related 28-day mortality (%)	21.3	27.7	0.631
Microbiological eradication (%)			
First 72 h	90.7	58.1	0.001
End of study treatment	100	81.2	0.01
Adverse events (%)			
Acute kidney injury (RIFLE)	53.4	59.6	0.679
Abnormal liver function test	12.8	12.8	1.000

(Continued on following page)

TABLE 1 (Continued)

Patient characteristic with/without carbapenem treatment	Colistin + fosfomycin	Colistin	*P* value
Outcomes of the study after excluding patients who received concurrent carbapenem			
n	43	39	
Favorable clinical response (%)			
First 72 h	76.7	66.7	0.336
End of study treatment	62.8	56.4	0.654
28-day all-cause mortality (%)	44.2	53.8	0.507
Infection-related 28-day mortality (%)	16.3	23.1	0.578
Microbiological eradication (%)			
First 72 h	87.8	65.7	0.028
End of study treatment	100	84.5	0.023
Adverse events (%)			
Acute kidney injury (RIFLE)[e]	37.2	48.7	0.372
Abnormal liver function test	11.6	15.4	0.749

[a] min, minimum; max, maximum.
[b] MRSA, methicillin-resistant *Staphylococcus aureus*.
[c] Other organisms, *Candida* spp. and *Stenotrophomonas maltophilia*.
[d] Other antibiotics, levofloxacin, metronidazole, and amphotericin B.
[e] RIFLE is a classification representing risk, injury, failure, loss of kidney function, and end-stage kidney disease.

baumannii infection treated with colistin was 46% (2). Assuming the combination therapy reduced the 28-day mortality by 50%, from 46% to 23% compared with therapy with colistin alone, 46 patients per group were needed when 5% type I error and 20% type II error were accepted. The data were analyzed by descriptive statistics, unpaired Student's *t* test, chi-square test, or Fisher's exact test, where appropriate. Survival analysis was performed by the Breslow test. A *P* value of ≤0.05 was considered statistically significant.

Ninety-nine patients were enrolled in the study, and five patients were excluded from data analysis because the causative organism was not *A. baumannii*, the causative organism was a carbapenem-susceptible isolate, or the patient died within 24 h after enrollment. Therefore, there were 94 patients included in the data analyses, i.e., 47 patients in the monotherapy group and 47 patients in the combination group. The characteristics and the outcomes of the 94 study patients are summarized in Table 1. The characteristics of the patients in both groups were comparable. Most of the study patients were elderly, had chronic underlying diseases, received mechanical ventilators, and developed ventilator-associated pneumonia (VAP). Favorable clinical outcomes, mortality at the end of study treatment, and mortality at 28 days were not significantly different. A survival analysis showed no significant difference in survival time between the patients who received combination therapy and monotherapy ($P = 0.656$). However, the microbiological eradication rates in the combination group were significantly higher than those in the monotherapy group, at 90.7% versus 58.1% at the first 72 h, and 100% versus 81.2%, respectively, at the end of study treatment. Renal impairment was observed in 53.4% and 59.6% of the combination and monotherapy groups, respectively. The patients tolerated the combination of colistin and fosfomycin therapy well. No neurotoxicity was observed related to the study treatments. The outcomes of the study when the patients who received concurrent carbapenem were excluded were similar to the overall treatment outcomes, as shown in Table 1.

The average dose ± standard deviation of colistin given to all subjects was 4.2 ± 1.5 mg/kg/day, and the average doses of colistin given to the patients in both groups were not significantly different from those shown in Table 1. Such a dose might achieve an average concentration of colistin in plasma around 2 μg/ml at steady state (9). Although the MIC_{90}s of almost all CR *A. baumannii* isolates are <2 μg/ml, many patients might have much lower colistin concentration in their plasma. Moreover, most of the study patients had VAP, and the concentration of colistin in the lung tissue should be lower than that in plasma, as Imberti et al. (10) reported that the concentrations of colistin in the bronchoalveolar lavage fluid were undetectable after the intravenous administration of colistin (10). Four grams of parenteral fosfomycin every 12 h might achieve a peak concentration in plasma of >260 μg/ml, which is much higher than the MIC_{90}s of almost all CR *A. baumannii* isolates (11). Fosfomycin penetrates the fluid of the interstitial space of soft tissues and reaches levels sufficient to inhibit the growth of bacteria at the target site (12). The aforementioned information might contribute to observing significantly more microbiological responses in the combination group than in the monotherapy group. However, a reduction in the mortality of patients in the combination group was not detected. Only a trend of greater clinical response (absolute difference, 12.3% at the first 72 h and 4.3% at the end of treatment) and a trend of lower mortality (absolute difference, 10.6% for overall 28-day mortality and 6.4% for infection-related 28-day mortality) in the combination group compared with the monotherapy group were observed. Several reasons might explain nonsignificant differences in the clinical outcomes. Most of the study patients had severe infection due to VAP, with a mean Acute Physiology and Chronic Health Evaluation (APACHE) II score at diagnosis of infection of 22 to 23. APACHE II score has been shown to be an independent predictor of mortality due to VAP, and patients with an APACHE II score of >16 had 54% mortality even though they received appropriate antibiotics (13). Intravenous fosfomycin given at 12-h intervals might not be sufficiently frequent to achieve maximum

bactericidal effect, since its serum half-life is only 2 h (11). The sample size of the subjects in this study was not large enough to detect a 10% difference in mortality, and approximately 3,000 patients would be needed in order to detect such a small yet significant difference in mortality. Since this study was unable to identify any subgroup of patients with CR *A. baumannii* infections who might gain clinical benefit from receiving combination therapy, the addition of fosfomycin to colistin for therapy of against CR *A. baumannii* infection is not generally recommended at this time. A multicenter study of many more patients is required to determine if the combination of fosfomycin and colistin is more beneficial than colistin alone in lowering the mortality rate of patients infected with CR *A. baumannii*.

ACKNOWLEDGMENTS

We thank the faculty of medicine at Siriraj Hospital, Infectious Disease Association of Thailand, and Health Systems Research Institute (Thailand) for supporting the study. We also thank Pornpan Koomanachai for study coordination and Sasima Tongsai for data analyses.

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