Clinical experience with colistin in 9 Japanese patients with infection due to multi-drug resistance pathogens

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Colistin is a polypeptide antibiotic of the polymyxin family (polymyxin E) which has been reported to be active against many multidrug-resistant (MDR) Gram-negative aerobic bacteria collected across the globe. While this agent was not currently licensed in Japan, the emergence of MDR organisms has necessitated its off-label used in the country. However, colistin was approved in March, 2015. This retrospective observational report includes nine patients with MDR Gram-negative infections due to *Pseudomonas aeruginosa* (n＝6) and *Klebsiella* spp. (n＝3) who received intravenous colistin therapy as part of their antimicrobial regimen. The median age and duration of administration were 40 years (range 7-90) and 8 days (range 1-19). Clinical success was observed in all eight patients for whom efficacy could be evaluated. Two patients encountered colistin related adverse effects 22.2% (2/9). In both cases the nephrotoxicity and dysgeusia resolved after discontinuation of colistin therapy. *In vitro* studies conducted with these clinical isolates of *P. aeruginosa* displayed synergy with the combination of colistin plus ceftazidime, rifampicin, meropenem or aztreonam. This report provides early evidence that colistin is generally safe, effective and demonstrates *in vitro* synergy when used in combination for the management of MDR Gram-negative pathogens derived from Japanese patients.

Introduction

Colistin is a polypeptide antibiotic of the polymyxin family (polymyxin E) which is active against most Gram-negative aerobic bacteria, including those displaying resistance to other parenteral antibiotics used in the hospital setting. As a result of emerging resistance in Gram-nega-

tive bacteria and the lack of new medicinal entities, previously discovered agents like colistin are being increasingly utilized for the management of infection due to multi-drug resistant (MDR) pathogens. While colistin has demonstrated *in vitro* potency against organisms displaying the MDR phenotype (i.e., resistance to three classes of antibiotics), the adverse event profile, notably nephrotoxicity and neurotoxicity, has limited the widespread general use of this agent. Moreover, the lack of a full understanding of how best to optimize the pharmacodynamic and minimize the toxicodynamic profiles of this agent has also tempered the use of colistin in all but the sickest patient populations who have previous failed conventional therapeutic approaches[1)].

Patients and Methods

Prior to the initiation of the study, the methodology was reviewed and approved by the ethical committee of Aichi Medical University (approval number 11-055). A retrospective review was performed on all patients at Aichi Medical University Hospital who received intravenous colistin for the treatment of resistant Gram-negative bacteria from November 2011 to April 2013. All patients provided written informed consent before inclusion in the study.

During this study period, colistin was prescribed as colistimethate for injection (Coly-Mycin®, each vial of colistimethate for injection contains 150 mg), which is a pro-drug that is hydrolyzed *in vivo* to the active form, colistin. The dosing of colistin in these patients was based on the practical guide for appropriate use of colistin in Japan[2)]. This guidance corresponded with package insert recommendations for both the mg/kg dosing and renal function adjustments.

Microbiological susceptibility assessments were performed using a microdilution method on the RAISUS system (Rapid Analyzer for Identification and Susceptibility test system, Nissui Pharmaceutical, Tokyo, Japan). The antibacterial activities of colistin, piperacillin, rifampicin, ceftazidime, aztreonam, meropenem, amikacin and ciprofloxacin were examined alone or in combination. Susceptibility testing and interpretation followed the recommendations of the CLSI[3)]. If the organism was determined to be MDR by RAISUS, additional checkerboard studies were undertaken using a commercially available “Break-point Checkerboard Plate” (Eiken Chemical, Tokyo, Japan)[4)].

Results

The evaluation of effectiveness in this study was based on the clinical outcome of the patient. Over the study period, a total of 9 patients (including two children) were administered colistin

owing to infection with MDR Gram-negative bacteria after informed consent had been obtained. When adverse events appeared the time course of the event, severity and potential relationship with colistin therapy were investigated. Nephrotoxicity was defined as a serum creatinine level of ＞0.5 mg/dL or ＞50% more than the value at study entry.

The demographics of the patient population are displayed in Table 1. This population included seven adults and two children with the primary infection source identified as the lung (n＝3), blood (n＝3), urinary tract (n＝2), bile and soft tissue (n＝1). The infecting MDR pathogens were *Pseudomonas aeruginosa* (n＝6) including one metallo-beta-lactamase producer, *Klebsiella pneumoniae* (n＝2) and one isolate of *Klebsiella oxytoca*. Colistin was administered for an average of 8.8 days (range 1-19) in combination with beta-lactam therapy as noted in the Table 1. MIC range of colistin was 0.125-2 mg/L. As defined by dosing guidelines the patients with normal renal function received 2.5 mg/kg in two divided doses daily, while dose adjustments were made for those with reductions in creatinine clearance.[2)]

Clinical success was observed in all eight patients for whom efficacy could be evaluated. Since the fourth patient only received one day of colistin therapy prior to his death which was attributed to pneumonia, an assessment of colistin efficacy for MDR infection in this patient was not possible. After the successful clinical response to infection, a eighth patient was also noted to expire due to acute lymphocytic leukemia.

Two patient encountered colistin related adverse effects 22.2% (2/9). In the patient with burn related injuries withdrawal of colistin was deemed necessary on day 4 of therapy due to elevations of serum creatinine to 2.70 mg/dL and blood urea nitrogen (BUN) to 23.4 mg/dL as noted in Figure 1A. Once colistin was discontinued the patient's renal function returned to normal in three days. The other patient experienced dysgeusia which presented 2 days after colistin therapy was initiated and resolved after colistin was stopped (Fig. 1B).

In addition to the clinical outcomes, the synergistic potential of combination therapy was also assessed in the present study for the pseudomonal isolates. Despite the MDR profile of the *P. aeruginosa* isolated from these patients, sufficiently high degrees of synergy were observed with colistin when combined with ceftazidime, rifampicin, meropenem or aztreonam (Fig. 2).

Discussion

Recently, a few case reports have provided data regarding the efficacy of colistin against MDR *P. aeruginosa* originating from Japanese patients[5,6)]. Since intravenous colistin is not approved for use in Japan, combination therapy is mandated when this agent is utilized. It is for

Table 1. Patient demography, antimicrobial utilization and outcomes with colistin therapy

Patients number	Age (years)	Gender	Primary diagnosis	Infection	MDR organisms	Source	MIC of CL (mg/L)	Dosage (mg/kg/day)	Duration (days)	Total dose (mg)	Combination of antibiotics	Clinical outcome	Adverse effects
1	7	Male	Anastomosis injury	Ventilator-associated pneumonia	*Pseudomonas aeruginosa*	sputum	0.5	2.8	10	500	BIPM	Success	No observed
2	62	Male	Heart failure	Pyelonephritis	*Pseudomonas aeruginosa*	urine	0.5	2.4	8	1080	BIPM	Success	Dysgeusia (Paresthesia)
3	90	Male	Heart failure	Aspiration pneumonitis	*Pseudomonas aeruginosa*	sputum	2	1.6	10	640	BIPM	Success	No observed
4	89	Male	Pneumonia	Aspiration pneumonitis	*Pseudomonas aeruginosa*	sputum	2	2.5	1	160	CAZ	Died Not evaluable*	No observed
5	85	Male	Prostatomegaly	Cystitis	*Pseudomonas aeruginosa*	urine	0.5	1.3	6	360	BIPM	Success	No observed
6	25	Male	Burn injury	Skin and soft tissue infection	*Pseudomonas aeruginosa* (MBL-producing)	skin	0.5	2.5	6.5	3400	PIPC	Success	Renal dysfunction
7	40	Male	Sever acute pancreatitis	Sepsis	*Klebsiella oxytoca*	bile/ blood	1 / 0.125	1.8	8	960	PIPC/TAZ	Success	No observed
8	37	Male	Acute lymphocytic leukemia	Sepsis	*Klebsiella pneumoniae*	blood	0.5	1.3	11	770	BIPM	Success Died - non infection	No observed
9	7	Male	Anastomosis injury	Sepsis	*Klebsiella pneumoniae*	blood	0.125	2.8	19	1425	BIPM	Success	No observed

MDR: multidrug-resistant; MBL: metallo-beta-lactamase-producing; CL: colistin; BIPM: biapenem; CAZ: ceftazidime; PIPC/TAZ: piperacillin/tazobactam; PIPC: piperacillin; *Outcome could not be evaluated because patient received only 1 day of colistin therapy

Fig. 1. Presentation time-course of colistin-related adverse events: (A) nephrotoxicity in Case 6, (B) dysgeusia in Case 2

Fig. 1A

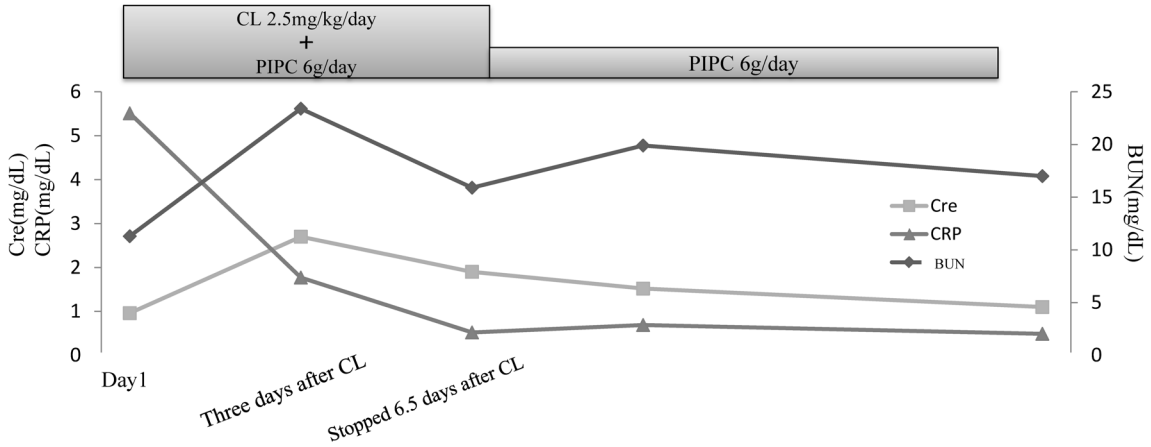
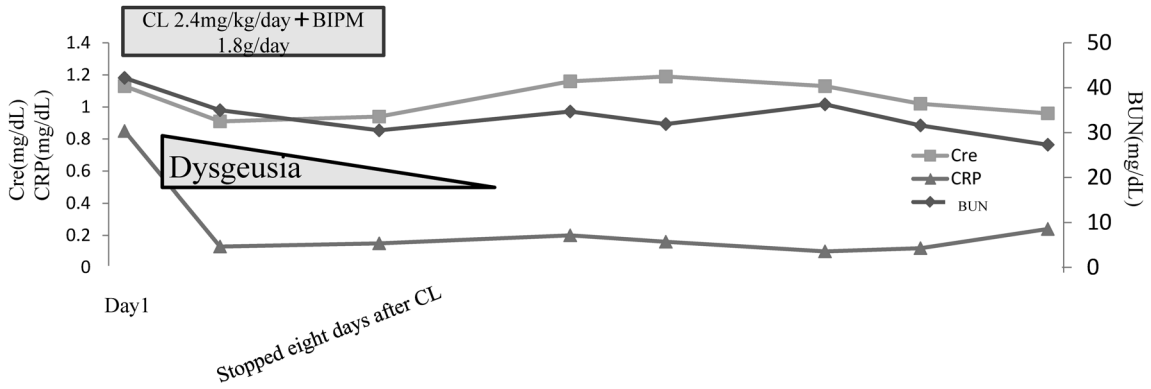


Fig. 1B



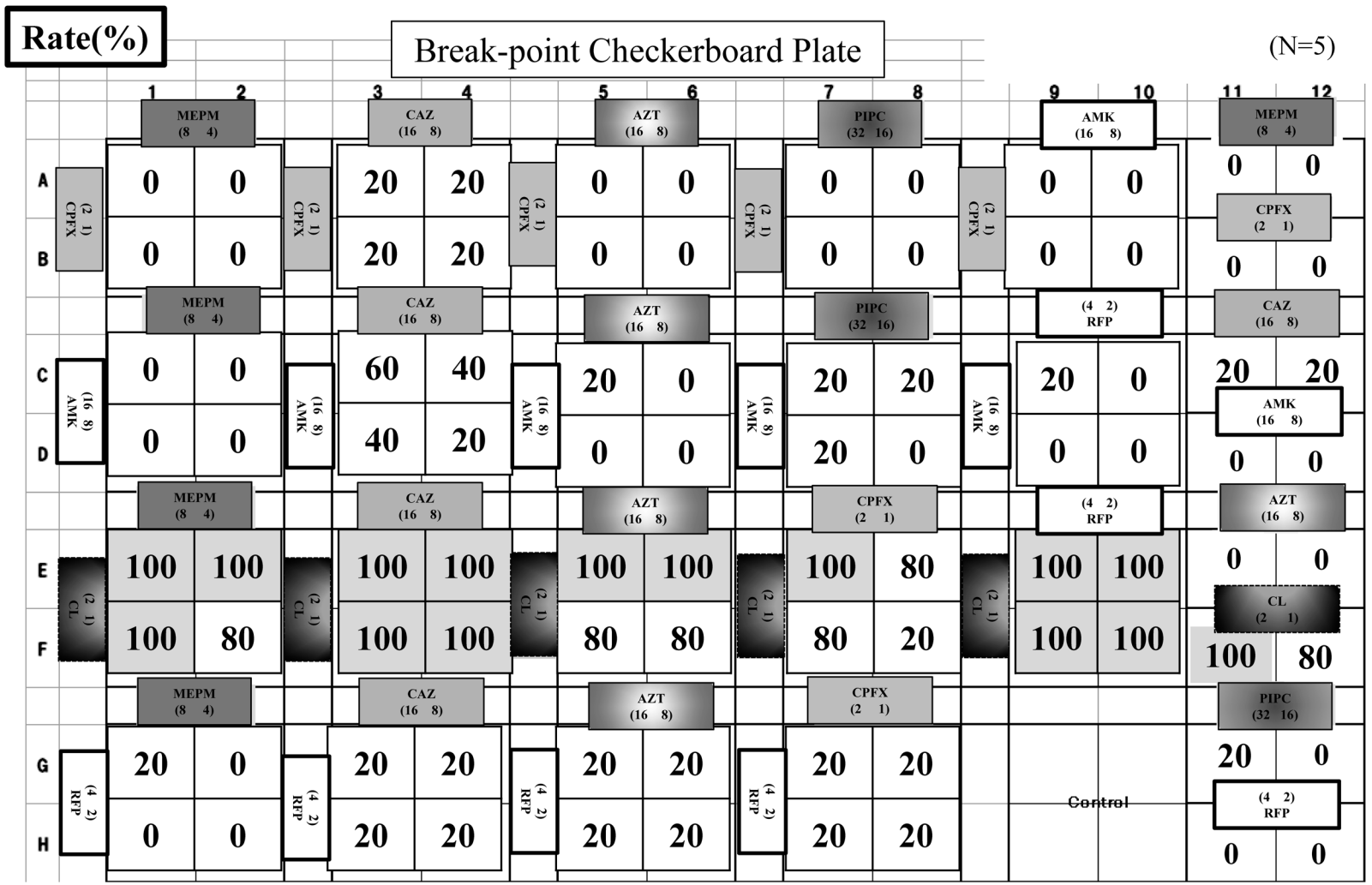
Abbreviations: Cre: serum creatinine; BUN: blood urea nitrogen; CRP: C-reactive protein; CL: colistin; BIPM: biapenem; PIPC: piperacillin

this reason that each of our patients received concomitant beta-lactam therapy, the majority (6/9) were given biapenem. While meropenem displayed *in vitro* synergy using the commercially available testing plate, biapenem was used in the clinical setting because of is susceptible profile by RAISUS and the fact that this agent is the least affected carbapenem analogue with metallo-beta-lactamase (MBL)s when compared to doripenem, imipenem and meropenem[7]. Moreover, biapenem displays the lowest MICs for Enterobacteriaceae with OXA-48 enzyme, *Acinetobacter* spp. with OXA-type carbapenemases, and has a similar MIC distribution to other carbapenems for isolates porin loss, AmpC or extended spectrum β-lactamase (ESBL) mediated resistance[7].

Several reports including the current study have demonstrated the nephrotoxic potential of colistimethate sodium[8~10]. While the authors have related this toxicity to the total cumulative

Fig. 2. Assessment of antibiotic synergy for multidrug-resistant *P. aeruginosa*

Antibiotic combinations and concentrations were designed in 96-well microplate, as shown in Fig. 2, in which synergistic effects were demonstrated in several combinations of antibiotics



Abbreviations: CPFX: ciprofloxacin; AMK: amikacin; CL: colistin; PIPC: piperacillin; RFP: rifampicin; CAZ: ceftazidime; AZT: aztreonam; MEPM: meropenem
Checkerboard plate with colistin in MDRP of 5 patients'. The values given in parentheses were each of drug's MIC and values of 0–100 were sensitive rates (%).

dose, utilization of a higher mg/kg dose, and duration of therapy, other investigators have not shown such associations[11,12]. As a result of this potential toxic event, Hartzell, J. D. *et al.* have suggested that providers need to be prudent in monitoring serum creatinine levels in patients given colistimethate sodium especially if prolonged courses are required[13]. Although kidney related toxicity is generally observed with prolonged exposure, toxicity has also been observed within the first 5 days of treatment[14] which is similar to the time course in our patient (Fig. 1).

While arbekacin inhalation therapy may be an important therapeutic option for patients suffering with for MDR Gram-negative pneumonia in situations where systemic therapy alone is likely to be inadequate or systemic exposure will result in elevated toxicity, this approach is not suitable for the management of extrapulmonary infections[15]. Thus expanded therapeutic approaches will be required for the optimal management of these MDR infections. While new beta-lactam/beta-lactamase inhibitor combinations hold great promise, their lack of commercial availability makes our study of colistin in Japanese patients of great clinical value. Although our study is limited by the small number of patients with MDR organisms, the experience gained from these observations is important when taken with the currently available efficacy and toxicity data accumulated in country with colistin.

In conclusion, our study shows that colistin appears to be generally safe and effective in a cohort of Japanese patients with limited therapeutic options. While colistin is increasingly being utilized for the treatment of MDR Gram-negative infections within Japan, dosing varies greatly and additional study is required to determine the optimal regimen.

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