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High Dose, Extended-Interval Colistin Administration in Critically Ill Patients: Is this the Right Dosing Strategy? A Preliminary Study

Lidia Dalfino[1], Filomena Puntillo[1], Adriana Mosca[2], Rosa Monno[2], Maria Luigia Spada[1], Sara Coppolecchia[1], Giuseppe Miragliotta[2], Francesco Bruno[1], Nicola Brienza[1]

[1]Anesthesia and Intensive Care Unit, Department of Emergency and Organ Transplantation, University of Bari, Piazza G. Cesare 11, 70124 Bari, Italy.

[2] Microbiology Section, Department of Emergency and Organ Transplantation, University of Bari, Piazza G. Cesare 11, 70124 Bari, Italy.

Corresponding author

Lidia Dalfino, MD, Anesthesia and Intensive Care Unit, Department of Emergency and Organ Transplantation, University of Bari, Piazza G. Cesare 11, 70124 Bari, Italy.

E-mail address ldalfino@tiscali.it

Summary. In critically ill patients with otherwise untreatable nosocomial infections due to colistin-only susceptible gram-negatives, a *high dose-extended intervals* colistin dosing regimen, according to the PK/PD behaviour of the drug, is associated with low renal toxicity and high efficacy.

ABSTRACT

Background. Colistin-only susceptible (COS) Gram Negative Bacteria (GNB) are emerging causes of severe nosocomial infections, reviving interest in the use of colistin. However, consensus on the most effective way to administer colistin has not yet been reached.

Methods. All patients with sepsis due to COS or minimally susceptible GNB, who received intravenous colistin were prospectically enrolled. Colistimethate sodium (CMS) dosing schedule was based on a loading dose of 9 MU, and a 9 MU two-daily fractioned maintenance dose, titrated on renal function. For each CMS course, clinical cure, bacteriological clearance, daily serum creatinine and estimated creatinine clearance were recorded.

Results. Twenty-eight infectious episodes due to *A. baumannii* (46.4%), *K. pneumoniae* (46.4%), and *P. aeruginosa* (7.2%) were analyzed. Main types of infection were bloodstream infections (64.3%) and ventilator-associated pneumonia (35.7%). Clinical cure was observed in 23 (82.1%) cases. Acute kidney injury developed during 5 treatment courses (17.8%), did not require renal replacement therapy, and subsided within 10 days from CMS discontinuation. No correlation was found between serum creatinine variation (baseline-peak) and daily and cumulative doses of CMS, and between serum creatinine variation (baseline-peak) and duration of CMS treatment.

Conclusions. Our study shows that in severe infections by COS-GNB, the high-dose extended interval CMS regimen has a high efficacy, without significant renal toxicity.

INTRODUCTION

Severe nosocomial infections due to multidrug-resistant (MDR) gram-negative bacteria (GNB) account for high morbidity and mortality [1]. The increasing incidence of these strains and the lack of effective antimicrobials in the drug development pipeline [2] has led to a rekindled interest in the use of colistin as 'lastline' therapy [3]. However, *in vitro* efficacy of colistin against MDR *Pseudomonas aeruginosa, Acinetobacter baumannii* and *Klebsiella pneumoniae* (97%, 96% and 88%, respectively)[4] does not entail clinical cure, which in severe infections due to colistin-only susceptible (COS) strains ranges from 15% to 75% [5-14]. Although this wide range of *in vivo* efficacy mainly depends on substantial heterogeneity of illness severity, the role of dosing regimen must be taken into account. The benefit of administering the *right* drug is often nullified by a suboptimal exposure at the infection site due to inadequate dosage. Despite over 50 years of clinical use, consensus on the most effective colistin dosage has not yet been reached [3]. Colistin exhibits a concentration-dependent bactericidal activity, and its therapeutic efficacy strictly depends on peak/MIC or AUC/MIC ratio [15,16]. In critically ill patients, current colistin dosing regimens result both in sub-therapeutic peak concentration with respect to MDR-GNB MIC breakpoints [17-20] and in prolonged time to steady-state [19,20], leading to sub-optimal and delayed effective treatment. Therefore, higher dose and longer dosing interval strategy, along with a loading dose, have been proposed to obtain a more effective killing [17-21]. However, clinical efficacy and renal toxicity of such regimen remain to be tested.

The purpose of this study was to test the renal toxicity along with efficacy of a *salvage* therapy with a high-dose and extended-interval dosing regimen of colistin, in a cohort of critically ill patients with nosocomial infections due to COS-GNB.

METHODS

Study population and data collection. A prospective, observational, cohort study was performed from August 2010 to June 2011 in a 16-beds general ICU of a teaching hospital. All critically ill patients with sepsis due to COS or *minimally susceptible* GNB, who were administered intravenous colistin as a *rescue* therapy, were enrolled. Patients were excluded if they were <18 years old, pregnant or breast-feeding, or if received colistin treatment for less than 72 hours. Patients who after a cured infectious episode received a second colistin course due to different COS-GNB infection were considered as two different cases. Patients were followed up until ICU discharge or death.

Primary outcomes were colistin nephrotoxicity and efficacy.

A standardized case form was used to record patient characteristics, including age, gender, weight, underlying comorbidities (evaluated by Charlson Comorbidity Index), Acute Physiology and Chronic Health Evaluation (APACHE) II score on admission, Sequential Organ Failure Assessment (SOFA) score on enrolment, type of infection, causative organism and *in vitro* susceptibility, daily doses and duration of colistin therapy, cumulative dose of colistin, co-administered antibiotics, nephrotoxic agents (aminoglycosides, vancomycin, non-steroidal anti-inflammatory drugs, intravenous radiocontrast agent, diuretics, mannitol), clinical and microbiological responses to therapy.

Definitions and microbiological testing. *Infections* were defined according to Center for Disease Control and Prevention (CDC) [22]. *Ventilator-associated pneumonia* (VAP) was defined according to ATS/IDSA guidelines [23], and its bacteriological diagnosis required at least 10^6 cfu/ml in a quantitative tracheal aspirate culture. *Sepsis*, *severe sepsis* and *septic shock* were defined according to the ACCP/SCCM consensus conference criteria [24].

Follow-up specimens from tracheal aspirate, urines, blood and other suspected sites of infection were obtained two-times weekly and, when clinically indicated, from start of

CMS therapy until discharge or death. Identification of all causative microorganisms was based on routine microbiological methods. Antimicrobial susceptibility testing was performed by MicroScan Walkaway System using 42 GNC panels (Siemens, New York, NY) and breakpoints were those defined by the Clinical and Laboratory Standards Institute (CLSI) [25]. Susceptibility to colistin was determined by E test methodology (BioMerieux, France) using cation adjusted Mueller Hinton agar and the isolates were considered susceptible if MIC value was ≤ 2 mg/L [25].

An isolate was defined as *COS* if it was fully susceptible to colistin but resistant to antipseudomonal penicillins, cephalosporins, carbapenems, monobactams, quinolones, and aminoglycosides. MDR isolates fully susceptible to colistin and with full or intermediate susceptibility to aminoglycosides were considered *minimally susceptible* to antibiotics [11].

Colistin administration. Colistin was administered as colistimethate sodium (CMS) (Colomycin®, Forest Laboratories UK LTB, Bextley DA5 1 NX, UK), dissolved in 100-ml sterile saline, and administered over 30 minutes.

According to recent data [8,15,17-21], patients received a loading CMS dose of 9 MU, followed by a maintenance dose of 4.5 MU every 12 hrs. In patients with moderate-severe renal impairment (creatinine clearance (CrCl) < 50 ml/min), dose and dosing intervals adjustments were made according to Cockcroft and Gault creatinine clearance estimates: after a loading dose of 9 MU, maintenance doses of 4.5 MU/24 hrs for CrCl in the 20-50 ml/min range and of 4.5 MU/48 hrs for CrCl < 20 ml/min were administered.

Efficacy and nephrotoxicity assessment. Efficacy was evaluated by both clinical and bacteriological responses to therapy. *Clinical cure* or *failure* were defined as resolution or persistence/worsening of symptoms and signs of infection, respectively. *Bacteriological clearance* and *failure* were defined by eradication or by persistence of COS-GNB isolates

on follow-up cultures respectively, regardless of the clinical outcome of infection. Two independent investigators evaluated type of infection and outcome.

Daily serum creatinine (S_{CR}) and estimated CrCl were recorded from the first day of CMS therapy until discharge or death. Baseline GFR was calculated by the abbreviated Modification of Diet in the Renal Disease equation [26]. In patients with normal renal function (baseline S_{CR} < 1.2 mg/dl or GFR ≥ 50 ml/min/1.73 m^2), nephrotoxicity was defined as doubling of baseline S_{CR} level or drop in baseline CrCl by ≥ 50%, while in patients with baseline renal dysfunction (S_{CR} ≥ 1.2 mg/dl or GFR < 50 ml/min/1.73 m^2) nephrotoxicity was defined as an increase by > 50% of the baseline S_{CR} level, a decrease by ≥ 20% of calculated serum CrCl from baseline, or need of renal replacement therapy (RRT)[7,9]. Criteria need to be fulfilled for at least two consecutive determinations 24 hours apart, after two or more days of CMS therapy. The Acute Kidney Injury Network (AKIN) criteria [27] were used to evaluate the severity of acute kidney injury (AKI).

Statistical analysis. Serum creatinine and creatinine clearance at *baseline (*start of CMS therapy), *peak* (worst level reached during treatment), *stop CMS* (end of CMS therapy), and *final* (end of follow-up) time points were considered for statistical analysis. Continuous normally distributed data are expressed as mean ± standard deviation (SD) and compared using unpaired Student's t-test. Non-normally distributed data are expressed as median and 25% to 75% interquartile range (IQR) and compared using the Mann–Whitney U-test. Categorical data are expressed as number of events and percentage and compared by using the Fisher's exact test. A Pearson's regression analysis was performed to clarify the association between variables. In all comparisons, a *p*-value < 0.05 was considered statistically significant. Data were analysed using a Statistical Package from Social Sciences (SPSS, release 5.0.1 for Windows, Chicago) software.

RESULTS

Characteristics of the whole sample. Out of 28 critically ill patients who were prescribed colistin for COS-GNB infections, 3 patients were excluded due to colistin treatment duration below 72 hours (for 2 patients due to discharge and for one patient due to death). Three patients developed 2 infectious episodes due to different species of COS pathogens and were included as two different cases. Therefore, a total of 28 CMS treatments in 25 patients were analyzed.

Patients were predominantly males (75%), with a mean age of 65 (±18) years. Main comorbid conditions were hypertension (54.2%), ischemic heart disease (45.8%), diabetes mellitus (25%), chronic obstructive pulmonary disease (12.5%), and chronic kidney disease (8.3%). Mean Charlson comorbidity index was 2.7 (±1.8). Mean APACHE II score was 18 (±6). Mean SOFA score on day one of CMS therapy was 8 (±2). All patients were mechanically ventilated. Median onset time of first infectious episodes was 26 (IQR 18-48) days from ICU admission.

In 16 out of 28 (57.1%) infectious episodes clinical presentation was severe sepsis, while in the other 12 (42.9%) it was septic shock. BSI occurred in 18 (64.3%) cases, and VAP in the remaining 10 (35.7%) cases. Pathogens were *A. baumannii* in 13 (46.4%), *K. pneumoniae* in 13 (46.4%), and *P. aeruginosa* in 2 (7.2%) episodes. All strains were fully susceptible to colistin with MIC ranges of 0.19-1.5 mg/L, while 8 isolates of *K. pneumoniae* were susceptible also to gentamicin. Thus, 20 of the GNB isolates were COS, while the remaining 8 were considered as *minimally susceptible* strains.

In 14 (50%) episodes CMS was administered as monotherapy, and in 14 (50%) it was employed as combination therapy with aminoglycosides (69.2%) or carbapenems (30.8%).

Patients with normal baseline renal function (n=22; serum creatinine 0.7±0.2 mg/dl) received CMS at daily and cumulative doses of 8.5 (IQR 7.6-9) MU/day and 99 (IQR 69-126) MU/course, respectively. Median duration of treatment was 12 (IQR 10-17) days.

Patients with abnormal baseline renal function (n=6; serum creatinine 3.2±1.3 mg/dl) received a daily dose of medication of 6.7 (IQR 3.5-8) MU/day and a cumulative dose of 61 (IQR 28-89) MU/course. In this subset, median duration of CMS administration was 10.5 (IQR 8-18) days.

CMS efficacy. Clinical cure was obtained in 23 (82.1%) infectious episodes. Patients characteristics and clinical features of infectious episodes with favourable and unfavourable therapeutic response are summarized in table 1. Bacteriological clearance was achieved in 73.9% (n=17) of the cured infectious episodes, by the 3rd (IQR 1-5) day of CMS therapy in all BSI and by the 8th (IQR 3-10) day in 4 (40%) VAP episodes. No recurrent infection by the same multi-resistant pathogen was observed. Colistin resistance was never observed during the follow-up period. Breakthrough superinfections by intrinsically colistin-resistant organisms (*Serratia marcescens* and *Proteus mirabilis*) were observed in 2 patients on day 12 and 14 of CMS treatment.

CMS nephrotoxicity. No deterioration of renal function was observed during 23 CMS treatment courses (82.1%). In this subset, the not significant increase of serum creatinine levels observed during treatment (by 0.3 (IQR 0.12-0.57) mg/dl) returned at baseline at the end of the follow-up period (0.7 vs 0.7 mg/dl).

AKI developed during 5 CMS treatment courses (17.8%) in 5 different patients (one with pre-existing renal dysfunction), with an onset time of 7 (IQR 5.5-8.5) days. In these patients, S_{CR} at the beginning of therapy was 0.95 (IQR 0.59-1.37) mg/dl, and peaked at 4.1 (IQR 2.09-5.85; p=0.036 vs baseline) mg/dl in a median time of 4 (IQR 2.5-5) days. At the end of CMS therapy S_{CR} level was 3.73 (IQR 0.64-5) mg/dl, and dropped to 1.16 (IQR 0.55-3.68; p=053 vs baseline) mg/dl during follow-up, within 9.5 (IQR 7-13) days from CMS discontinuation. Temporal trends of estimated creatinine clearance in no AKI and AKI groups are reported in figure 1. All cases involved non-oliguric episodes, and in no

patients RRT was deemed necessary. One, two, and two patients met the criteria for AKI stages I, II, and III, respectively. All patients completed CMS therapy by dose reduction. Age (63.7±18 vs 72±8 years), Charlson index (2.2±1.6 vs 2.7±1.8), and Chronic kidney disease (22% vs 20%) did not differed between no AKI and AKI patients. Apart from radiocontrast agents, no significant predictor of renal impairment was found in univariate analysis (tab. 2).

In whole sample, no correlation was found between serum creatinine variation (baseline-peak percentage) and daily ($y = 1E\text{-}06x + 90.064$; $r = 0.0043$; $p = 0.98$) (fig. 2) and cumulative ($y = 0.0003x + 60.123$; $r = 0.06$; $p = 0.759$) doses of CMS, as well as between serum creatinine variation (baseline-peak percentage) and duration of CMS treatment ($y = -1.247x + 107.9$; $r = -0.058$; $p = 0.77$)(fig. 2).

DISCUSSION

The main finding of the present study is that in critically ill patients with life threatening nosocomial infections by gram-negative colistin-only susceptible bacteria (COS-GNB), a rescue therapy with a *high-dose extended-interval* dosing regimen of colistin provides a high degree of clinical cure, with no significant renal toxicity.

Currently, colistin-only susceptible *A. baumannii, P. aeruginosa, and K. pneumoniae* are emerging causes of severe nosocomial infections in intensive care unit (ICU) [28], and daily CMS total doses is directly related to clinical cure. Increasing daily dose from 2 MU [7] to 9 MU [5] improves clinical cure rates from 51% [7] to 70% [5]. However, not only daily dose, but also fractioning may affect efficacy. The 9 MU three-daily fractioned CMS regimen, currently prescribed in ICU practice, has been associated to suboptimal and delayed steady-state concentration [20,21]. Therefore, a loading dose to rapidly achieve target drug concentration and a dosing schedule using high single doses at longer intervals have been proposed [17,18,20,21]. According to this pharmacokinetic/pharmacodynamic

(PK/PD) background and to severity of infection, we adopted a dosing schedule based on a 9 MU loading CMS dose and a 4.5 MU/12-hours maintenance dose [21]. This regimen is consistent with data by Garonzik et al [20] who, on the basis of PK analysis of CMS and colistin in critically ill patients, suggest that in order to obtain a colistin steady state plasma concentration of 2.5 mg/L, a 70-kg patient with a CrCl of 80 ml/min (e.g.) needs to receive a CMS loading dose of 10 MU, followed by a maintenance CMS daily dose of 10 MU.

Our dosing regimen resulted in a 82% clinical cure rate, which is above the best favourable response rates reported in similar ICU settings with lower single-doses and/or more fractioned regimens [4-14]. Although the effectiveness of colistin in pneumonia has been questioned due to its inadequate lung diffusibility [9,14], in our cohort clinical cure was attained in 100% of VAP cases. The high single-dose CMS dosing strategy may have contributed to this high response rate, by increasing colistin concentration into the infected lung tissue. This hypothesis well fits with results of previous studies reporting a cure rate of only 57% in COS *P. aeruginosa* VAP treated with a 2.2-4.3 MU daily CMS regimen [9], and a cure rate of 75% in COS *A. baumannii* VAP episodes treated with 6 MU daily CMS regimen [14]. Of note, however, bacteriological clearance in VAP patients was only 40%. This low rate may reflect the well known persistent artificial and native airway colonization with *Enterobacteriaceae, A. baumannii* and *P. aeruginosa*, despite therapeutic success, and explain why clinical features and quantitative cultures of bronchial aspirate are the most relevant parameters in evaluating therapeutic response in patients with VAP [29].

Since current reported rates of renal failure may reach 50% [30,31], colistin-related nephrotoxicity still remains a major concern. Colistin induces tubular damage by increasing the epithelial cell membrane permeability, leading to leakage of contents and cell death [32]. This effect has been related to drug concentration and treatment duration [33,34], with significant relationship between creatinine increase and cumulative dose of

CMS [35]. In our study, *de novo* AKI was observed only in 18% of CMS courses, a percentage similar to those reported for lower single doses and more fractioned regimens of CMS [7,13,35]. Consistently with previous reports adopting the same AKI definition [7,10,22], in our sample AKI occurred early, was not severe, did not cause discontinuation of CMS, and subsided rapidly. Differently from other reports [34,35,36], in our study renal damage did not depend on daily CMS doses, on duration of treatment, or on cumulative CMS doses. Dose titration on the basis of renal function by prolonging dosing interval, instead of reducing single dose (according to colistin concentration-dependent pharmacodynamic behaviour), may have contributed to the low rate and moderate severity of AKI [20]. This well fits with a recent hypothesis [37], ascribing CMS nephrotoxicity to colistin minimum plasma concentration, as already demonstrated for aminoglycosides [38]. However, due to the relatively small number of patients, the study cannot provide an accurate estimate of the relative contribution of colistin to renal dysfunction. Other factors such as age, race and comorbidities, severity of critical illness, hemodynamic status and other potentially co-administered nephrotoxic agents, such as radiocontrast medium, may have played a crucial role in affecting kidney function. Nevertheless, even in presence of these favouring factors, AKI absolute rate was low.

Some points of the study need to be underlined. Although colistin monotherapy and extended dose interval regimens may promote colistin resistance in presence of colistin-heteroresistant GNB [15], in our study colistin monotherapy was employed in 50% of cases with no evidence of resistance emergence during and after CMS therapy discontinuation, as evaluated by surveillance coltures. Moreover, it is difficult to say whether the combination treatment with carbapenems or other active drugs played a more important role than giving a high dose of colistin. However, no differences were found in clinical cure for combination therapy regimens as compared to monotherapy, according to a recent comprehensive review [39].

Our study has some limitations. Despite the prospective design, the relatively small number of studied patients and the absence of a control group represent major limitations. Data on possible side-effects of colistin apart from nephrotoxicity were not evaluated actively. Finally, serum concentration of colistin were not measured and, therefore, we cannot draw any conclusion regarding peak levels reached with our dosing regimen. *Conclusions.* This study clearly shows that a 9 MU two-daily fractioned dosing regimen of colistin, along with a 9 MU loading dose, can be used with satisfactory efficacy and relatively low nephrotoxicity in life-threatening infections caused by COS-GNB, provided that an on-going adaption of dosing regimen to renal function is ensured. A multicentre study, with proper study design and a relevant control group, is needed to confirm these preliminary data, and to better define the relationships between colistin blood levels obtained by the *high dose extended interval* dosing strategy and renal toxicity.

Notes

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Table 1. *Patients characteristics and clinical features of infectious episodes with favourable and unfavourable therapeutic response.*

PATIENTS	**CURE** (n=21)	**FAILURE** (n=5)
Age (years), *ms±d*	62±18	76±3
Charlson comorbidity index, *ms±d*	2 (1.5)	3.2 (2.2)*
Surgical admission, *n (%)*	8 (36)	4 (80)
APACHE II score, *ms±d*	18±6	25±7*
SOFA score, *ms±d*	7.6±2	9.1±2
ICU LOS (days)	56 (30-85)	75 (52-86)
ICU Mortality, *n (%)*	5 (21.7)	5 (100)*
INFECTIOUS EPISODES	**CURE** (n=23)	**FAILURE** (n=5)
Onset time of infection (days)	22 (12-47)	42 (23-54)
BSI, *n (%)*	13 (56.5)	5 (100)
Pathogens, *n*		
A. baumannii	*6*	*2*
K. pneumoniae	*6*	*3*
P. aeruginosa	*1*	*0*
Bacteriological clearance, *n (%)*	13 (100)	0 (0)*
VAP, *n (%)*	10 (43.5)	0 (0)
Pathogens, *n*		
A. baumannii	*5*	*0*
K. pneumoniae	*4*	*0*
P. aeruginosa	*1*	*0*
Bacteriological clearance, *n (%)*	4 (40)	0 (0)
Clinical presentation, *n (%)*		
Severe sepsis	16 (69.5)	0 (0)*
Septic shock	7 (30.5)	5 (100)*
Daily CMS dose (MU/day)	8.5 (7.3-9)	7.7 (5-8.5)
Cumulative CMS dose (MU/course)	91 (61-122)	105 (17-142)
CMS Monotherapy, *n (%)*	12 (54.5)	2 (40)
CMS Treatment duration (days)	11 (10-14.5)	15.5 (7-21)

Data are expressed as median and IQ ranges, unless otherwise specified. **p <0.05 versus cured patients.* APACHE, Acute Physiology and Chronic Health Evaluation; LOS, length of stay; BSI, bloodstream infections; VAP, ventilator-associated pneumonia; CMS, colistimethate sodium; MU, million units.

Table 2. *Potential risk factors for renal impairment during CMS courses in no AKI and AKI groups*

	No AKI (n=23)	**AKI (n=5)**
Septic shock, n (%)	10 (43.5)	2 (40)
Concomitant Nephrotoxics, n (%)	20 (86.9)	4 (80)
Antibiotics	7 (30.4)	3 (48)
Diuretics	15 (65.2)	3 (48)
Radiocontrast agents	1 (4.3)	4 (80)*
Mannitol	4 (17.4)	1 (20)
Daily CMS dose, (MU/day)	8.3 (6.5-9)	7.1 (6-8.5)
CMS treatment duration (days)	11 (9.5-17.5)	12 (10-15)
Cumulative CMS dose	92 (56-126)	81 (64-92)

Data are expressed as median and IQ ranges, unless otherwise specified. *p <0.05 versus baseline. CMS, colistimethate sodium; AKI, acute kidney injury; MU, million units.

Figure legends

Figure 1. Estimated creatinine clearance median values on the first day of colistin treatment (baseline), at the lowest value reached (worst), on discontinuation of CMS treatment (stop CMS), and at the end of follow-up (final), in patients without (white boxplots), and with (gray boxplots) acute kidney injury (AKI). *p <0.05 versus baseline. CMS, colistimethate sodium; AKI, acute kidney injury.

Figure 2. Correlation between serum creatinine variation (baseline - peak values) and daily CMS doses (A), and between serum creatinine variation (baseline - peak values) and treatment duration (B). CMS, colistimethate sodium.

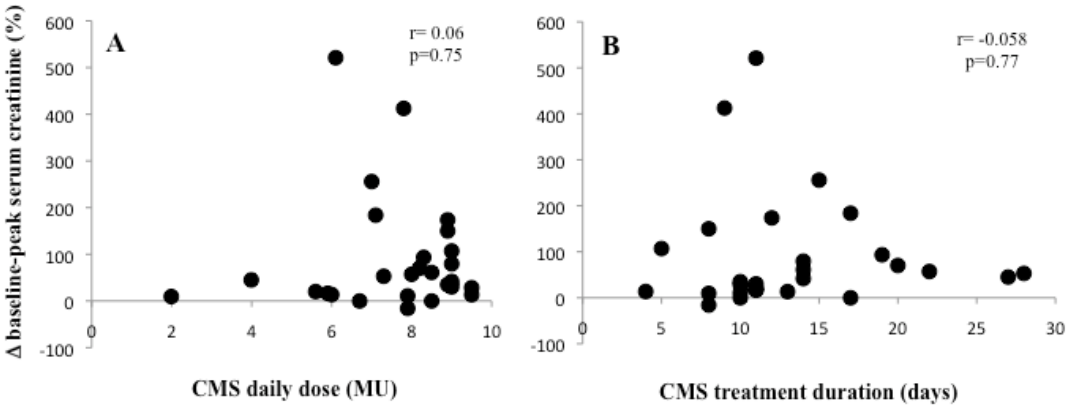

Fig. 1

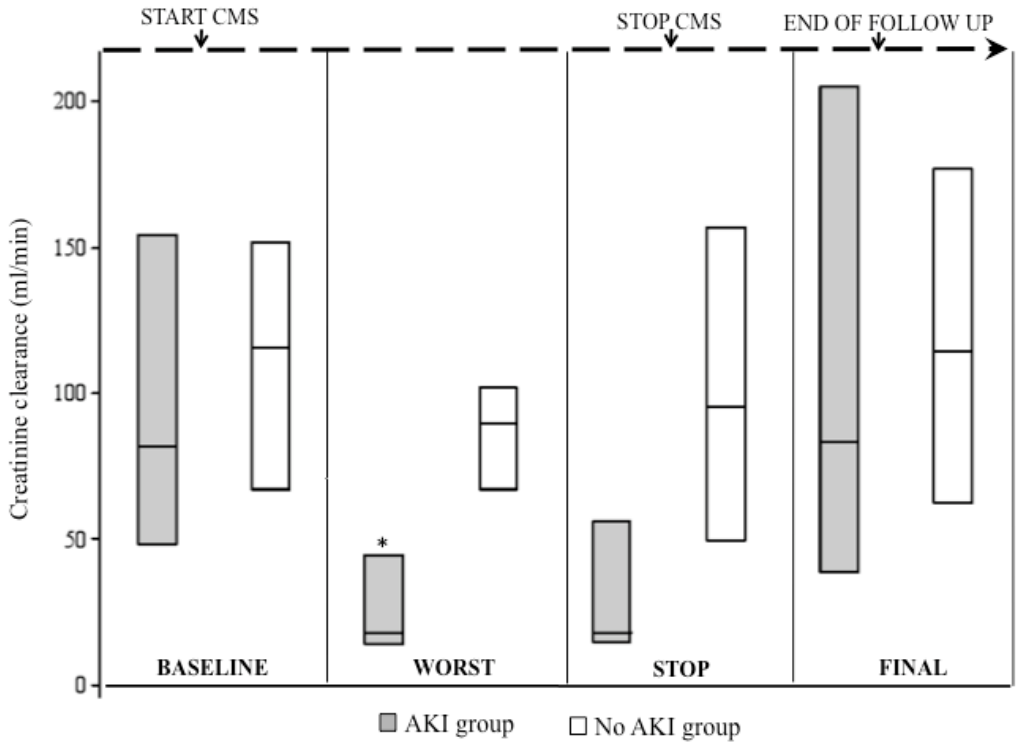

Fig. 2