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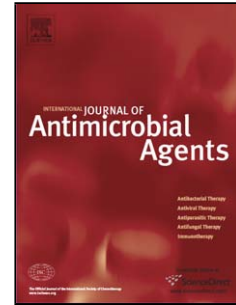
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# Colistin therapy for microbiologically documented multidrug-resistant Gram-negative bacterial infections: a retrospective cohort study of 258 patients

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## ABSTRACT

It is unclear whether the effectiveness of polymyxins depends on the site of infection, the responsible pathogen, dosage, and monotherapy versus combination therapy. We investigated colistin therapy in a large, retrospective, single-centre, cohort study. Primary analysis outcomes were infection outcome, survival and nephrotoxicity. Over a 7-year period (October 2000 to October 2007), 258 patients received intravenous (i.v.) colistin for at least 72 h for microbiologically documented multidrug-resistant Gram-negative bacterial infections, comprising 170 (65.9%) *Acinetobacter baumannii*, 68 (26.4%) *Pseudomonas aeruginosa*, 18 (7.0%) *Klebsiella pneumoniae*, 1 (0.4%) *Stenotrophomonas maltophilia* and 1 (0.4%) *Enterobacter cloacae*. Cure of infection occurred in 79.1% of patients, nephrotoxicity in 10% and hospital survival in 65.1%. In the multivariate analysis, independent predictors of survival were colistin average daily dose [adjusted odds ratio (aOR) = 1.22, 95% confidence interval (CI) 1.05–1.42] and cure of infection (aOR = 9, 95% CI 3.6–23.1), whilst the proportion of creatinine change (aOR = 0.21, 95% CI 0.1–0.45), Acute Physiology and Chronic Health Evaluation (APACHE) II score (aOR = 0.89, 95% CI 0.84–0.95) and haematological disease (aOR = 0.23, 95% CI 0.08–0.66) were associated with mortality. Effectiveness of colistin was not dependent on the type of pathogen. No independent predictors for nephrotoxicity were observed. The findings of the largest cohort study to date on i.v. colistin show that colistin is a valuable antibiotic with acceptable nephrotoxicity and considerable effectiveness that depends on the daily dosage and infection site.

## 1. Introduction

Management of infections due to multidrug-resistant (MDR) Gram-negative bacteria is part of regular clinical practice in many hospitals worldwide [1]. The relatively scarce production of new antibiotics against such infections has led physicians to the re-introduction of intravenous (i.v.) polymyxins (colistin and polymyxin B), an antibiotic class discovered more than 60 years ago that had been abandoned for nearly 20 years, except for in the distinct population of patients with cystic fibrosis [2]. A number of recently published clinical studies have suggested that colistin may be considered in the treatment of patients with MDR Gram-negative bacterial infections [3–9].

A number of questions regarding the clinical utility of polymyxins remain unanswered. Thus, we performed a large, retrospective, single-centre, cohort study of patients receiving i.v. colistin to investigate further various questions on the role of polymyxins in modern clinical practice. Specifically, we focused on questions regarding the effectiveness of colistin depending on dosage, combination treatment or monotherapy, infection site and pathogen.

## 2. Methods

### *2.1. Study design*

The study was approved by the review board of Henry Dunant Hospital (Athens, Greece). All patients receiving i.v. colistin for at least 72 h during a 7-year period (October 2000 to October 2007) for clinically diagnosed and microbiologically documented infections caused by MDR Gram-negative bacteria (resistant to at least two classes of relevant antibiotics) were eligible for inclusion. Only the first episode of MDR Gram-negative bacterial infection

treated with colistin was included in the analysis. An a priori decision was made not to remove from this analysis patients who received care during the period October 2000 to May 2005 for whom a subset of data has been reported previously [5–7]. Specifically, some data on 108 patients included in this analysis have been previously reported.

## *2.2. Microbiological assays*

Routine laboratory susceptibility testing procedures for commonly used antibiotics were performed with the use of an automated broth microdilution method (Vitek 2; bioMérieux, Hazelwood, MO). The susceptibility of the Gram-negative bacteria studied to colistin was determined using the colistin Etest strip (AB BIODISK, Solna, Sweden). Test results were interpreted as showing susceptibility of a bacterial isolate to colistin when the respective minimum inhibitory concentration was  $\leq 2$   $\mu\text{g/mL}$ .

## *2.3. Definition of infections and outcomes*

Differentiation between infection and colonisation with the studied isolates as well as determination of infection-related outcomes were performed independently by two investigators who were blinded to the specific regimen of colistin administered. Infection cure, mortality and nephrotoxicity depending on the specific colistin regimen and dosage were the main outcomes of this study. Nephrotoxicity was defined by an increase in serum creatinine level of more than 50% over the baseline level (recorded on the first day of i.v. colistin administration) at a value above the upper normal limit ( $>1.3$  mg/dL or 115  $\mu\text{mol/L}$ ) or by need for haemodialysis.

#### 2.4. Collection and extraction of data

For patients admitted to the Intensive Care Unit (ICU), the duration of stay was noted as well as the use and duration of mechanical ventilation; the Acute Physiology and Chronic Health Evaluation (APACHE) II score on admission was also calculated. Various clinical and laboratory variables were analysed as factors potentially associated with the outcomes defined above; such variables referred only to the index hospitalisation and up to the time point of isolation of the studied pathogens.

#### 2.5. Data analysis

Variables found to be significantly associated with outcomes in the univariate analyses were entered in a multivariate backward, stepwise, logistic regression model. Only patients who were admitted to the ICU and with an APACHE II score available were included in the final model. For all tests performed, a two-tailed *P*-value  $\leq 0.05$  was considered statistically significant.

### 3. Results

#### 3.1. Study population

In total, 258 patients [174 (67%) males] fulfilled the inclusion criteria. Among these, 222 patients (86%) were hospitalised in the ICU. The mean patient age was 61 years (range 15–98 years) and the mean APACHE II score was 17 (range 2–39). The mean duration of hospital and ICU stay until the start of colistin administration for the index infection was 18.3 days and 11.4 days, respectively [interquartile range (IQR) 7–21 days and 5–15 days, respectively]. The mean duration of colistin administration was 17.9 days (IQR 10–22 days). There were 170 (65.9%) *Acinetobacter baumannii* infections, 68 (26.4%)



*Pseudomonas aeruginosa*, 18 (7.0%) *Klebsiella pneumoniae*, 1 (0.4%) *Stenotrophomonas maltophilia* and 1 (0.4%) *Enterobacter cloacae*. The proportion of polymyxin-only-susceptible (POS) pathogens was 52.3% (135/258); the remainder were susceptible to colistin and at least one other antimicrobial agent. There were 155 cases of pneumonia (60%), 33 cases of bacteraemia (13%), 22 abdominal infections (9%), 16 central venous catheter-related infections (6%) and 32 infections of other sites (12%). The all-cause in-hospital mortality among patients included in this study was 34.9%.

### 3.2. Cure of infection analysis

Table 1 shows a comparison of the distribution of various characteristics between the groups of patients with or without cure of infection. The outcome of infection due to different pathogens varied widely according to the specific therapeutic regimen administered (Table 2). In total, infection was cured in 83.3% of patients who received colistin monotherapy or colistin combined with meropenem. In contrast, patients who were treated with colistin combined with piperacillin/tazobactam, ampicillin/sulbactam or other agents had significantly lower rates of infection cure (64.7%, 75.0% and 61.3%, respectively). Overall, colistin monotherapy did not differ significantly from the colistin/meropenem combination in terms of infection cure rate (Table 2).

Table 3 shows the findings from the multivariate logistic regression model for cure of infection (dependent variable). The adjusted odds ratios (aORs) provided by the final model equation showed that patients who received either colistin monotherapy or colistin/meropenem combination were more likely to be cured compared with patients who received colistin combined with some other agent. Furthermore, pneumonia was more frequently cured compared with other infections (mainly bacteraemia and abdominal

infections). On the other hand, increasing age and higher proportion of creatinine change during treatment were independently associated with failure to cure the infection.

### 3.3. Mortality analysis

The univariate analysis for all-cause in-hospital mortality showed that the group of patients who died had significantly higher age, APACHE II score and proportion of creatinine change as well as being treated with a significantly lower average daily dose of colistin ( $P = 0.011$ ) compared with the group of patients who survived. Mortality among patients who received an average colistin daily dose of 3 million international units (IU) (38.6%) was higher than mortality among patients who received 6 million IU (27.8%) and patients who received 9 million IU (21.7%). The above was also observed among patients who had baseline creatinine within normal values (34.3%, 27.6% and 19.5% mortality among patients who received an average colistin daily dose of 3, 6 and 9 million IU, respectively). Furthermore, malignancy, cardiovascular and haematological disease, blood transfusion, haemodialysis, failure to cure the infection and nephrotoxicity were significantly more frequent among patients who died. Finally, urinary tract infections caused by MDR Gram-negative bacteria and treated with colistin were less frequent among patients who died in this cohort.

Multivariate analysis of survival data showed that higher daily colistin dose [aOR = 1.22, 95% confidence interval (CI) 1.05–1.42;  $P = 0.009$ ] and cure of infection (aOR = 9, 95% CI 3.6–23.1;  $P < 0.001$ ) were associated with increased probability of survival. On the other hand, higher APACHE II score (aOR = 0.89, 95% CI 0.84–0.95;  $P < 0.001$ ) and proportional raise of creatinine (aOR = 0.21, 95% CI 0.1–0.45;  $P < 0.001$ ) as well as presence of haematological disease (aOR = 0.23, 95% CI 0.08–0.66;  $P = 0.006$ ) were independently associated with decreased probability of survival.

### 3.4. Nephrotoxicity analysis

None of the recorded clinical characteristics, including colistin average daily and cumulative dose, were associated with development of nephrotoxicity in this analysis.

### 3.5. Subset analysis for patients with polymyxin-only-susceptible infections

In a subset analysis of patients with infections caused by POS bacteria, 18 (90%) of 20 patients treated with colistin monotherapy were cured from the infection compared with 70 (83.3%) of 84 patients treated with colistin combined with meropenem and 17 (54.8%) of 31 patients treated with colistin combined with other antimicrobial agents ( $P = 0.002$ ). The multivariate model for cure of infection (dependent variable) for this subset of patients showed that treatment with colistin monotherapy or colistin/meropenem combination was an independent factor for cure of infection ( $P = 0.017$ ). On the other hand, presence of malignancy ( $P = 0.008$ ) and infections other than pneumonia ( $P = 0.006$ ) were independent risk factors for failure to cure the infection. The relevant multivariate analysis for mortality showed that deterioration of infection ( $P = 0.001$ ), APACHE II score ( $P = 0.002$ ), use of steroids ( $P = 0.001$ ) and proportion of creatinine raise ( $P < 0.001$ ) were independent risk factors for death.

## 4. Discussion

The main finding of this retrospective cohort analysis of patients receiving i.v. colistin for microbiologically documented infections is that independent factors for a favourable infection outcome were antimicrobial regimens that consisted of colistin monotherapy or colistin/meropenem combination therapy (compared with combination of colistin with other agents with potential activity against the isolated pathogens) and pneumonia (compared

mainly with bacteraemia and abdominal infections); age and proportion of creatinine change during treatment were independently associated with a unfavourable infection outcome. In addition, the average daily colistin dose and the infection outcome were independent factors for lower mortality, whilst APACHE II score, haematological disease and nephrotoxicity were independent factors for increased mortality. The analysis did not reveal any factor associated with nephrotoxicity.

It is noteworthy that the findings of the subset analysis performed in patients with a POS isolate corroborated the majority of the findings applying to the whole cohort. Colistin monotherapy or colistin/meropenem combination therapy were also independent factors associated with a better infection outcome in this subset of patients that made up 52.3% of the total number of patients included in this study; a favourable infection outcome was also independently associated with pneumonia. Infection outcome, APACHE II score and proportion of creatinine change were independent risk factors for mortality in this subset of patients.

Patients who were treated with colistin monotherapy or colistin/meropenem had a better infection outcome than patients who received colistin in combination with a different antibiotic. This finding is in keeping with data from in vitro studies on the synergistic effectiveness of colistin with meropenem [10–12]. Whilst our study did not show a difference in terms of effectiveness between the colistin monotherapy and colistin/meropenem combination groups, one has to be cautious regarding monotherapy as heteroresistance may arise when treating with colistin alone as shown in vitro [13,14]. On the other hand, one should be alert that combination regimens may neither confer a better clinical outcome nor prevent the emergence of resistance [15].

It is interesting that the average daily dose of colistin was an independent factor for mortality; there was a  $0.8 \times 10^6$  IU difference in the average colistin dose between survivors and deceased patients (survivors received a higher dose). It is interesting that the ideal dose of colistin has not yet been established through randomised controlled trials (RCTs). Scientific efforts have yielded considerable in vivo experimental pharmacodynamic and pharmacokinetic data regarding colistin during the last 5 years. Addressing the issue of what constitutes the appropriate dose has important clinical impact. Serum levels may not be sufficient when administering the relatively lower dose of colistin intravenously. In addition, underdosing of colistin may be important in the development of emergence of resistance.

This study is a 7-year cohort and various different doses of colistin were used. In the past, we would administer colistin at low doses, based on several reports regarding the nephrotoxicity of the drug. Time passing, we realised that the proportion of patients who developed nephrotoxicity during colistin treatment was lower than reported in the past. Thus, we started treating patients with higher daily doses of colistin administered intravenously, up to 720 mg (9 million IU) per day (in three divided doses), based on our experience as well as on reports by other groups. During the last 2 years, we have standardised our clinical treatment protocol to 9 million IU/day. Finally, it should be mentioned that colistin doses were adapted to renal function.

No significant difference was found between daily dose of colistin and cure of infection. This may be attributed to the fact that only the first episode (per patient) of MDR Gram-negative bacterial infection treated with colistin was included in the analysis. Thus, the cure of infection analysis refers to the first episode only. We believe that underdosing of colistin may be important in the development of emergence of resistance. Furthermore,

lower dosage may not eradicate the pathogen, resulting in recurrent infections and increased morbidity and mortality. Finally, our study may be underpowered and a larger sample or an RCT would better consolidate this trend.

In our patient cohort, colistin was more effective in the treatment of pneumonia compared with the treatment of other infection sites such as bacteraemia and abdominal infection. This may be explained by the fact that, still today, bacteraemia, regardless of the causative agent, remains the most severe threat to patients with infections.

This study has certain limitations. First, one has to acknowledge that, due to the innate limitations of retrospective studies, certain cases of colonisation may have been treated as clinical infections. Moreover, a significant proportion of our patients received colistin for infections due to MDR bacteria that were susceptible to colistin and up to two other classes of antibiotics and thus these patients could theoretically have been treated with a regimen not containing colistin. Another limitation is that susceptibility testing for sulbactam was not performed until 2005 and that pharmacodynamic study was not performed in our cohort of patients. Finally, data for certain adverse events of colistin, such as neurotoxicity and muscular weakness, were rather limited. We believe that despite these shortcomings, the findings of the study may be useful to clinicians and researchers since this cohort of patients who received colistin for microbiologically documented infections constitutes the largest worldwide until now, providing data on the effectiveness of colistin with regard to dosage, infection site, type of Gram-negative bacteria and combination antimicrobial therapy.

In conclusion, in this retrospective cohort study patients who received colistin monotherapy or colistin/meropenem combination had a better infection outcome than those who

received colistin in combination with other antibiotics. Moreover, patients with pneumonia had a better infection outcome compared with those with other infection types. Additionally, patients who received a higher average daily dose of colistin had a lower mortality. There was no difference regarding the effectiveness of colistin with regard to the specific type of Gram-negative bacterium (i.e. similar effectiveness in the treatment of infections due to *A. baumannii*, *P. aeruginosa* and *K. pneumoniae*). The necessity to conduct RCTs on colistin that will help further illuminate its role in clinical practice cannot be emphasised enough.

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### **Competing interests**

None.

### **Ethical approval**

Not required.

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**Table 1**

Univariate analysis for cure of infection

	Deterioration ( <i>N</i> = 54) [mean ± S.D. or <i>n</i> (%)]	Cure ( <i>N</i> = 204) [mean ± S.D. or <i>n</i> (%)]	<i>P</i> - value
<b>Demographics</b>			
Age (years)	66.6 ± 14.4	59.6 ± 19.1	0.039
Sex (male)	36 (66.7)	138 (67.6)	0.89
APACHE II score	18.9 ± 7.4	16.6 ± 6.5	0.047
<b>Co-morbidities</b>			
Malignancy	26 (48.1)	40 (19.6)	<0.001
Cardiovascular	27 (50.0)	97 (47.5)	0.75
Pulmonary	15 (27.8)	48 (23.5)	0.52
Diabetes mellitus	16 (29.6)	43 (21.1)	0.18
Urogenital <sup>a</sup>	9 (16.7)	38 (18.6)	0.74
Chronic renal failure	2 (3.7)	11 (5.4)	1.00
Hepatic	8 (14.8)	16 (7.8)	0.12
Haematological <sup>b</sup>	6 (11.1)	21 (10.3)	0.86
Neurological <sup>c</sup>	13 (24.1)	61 (29.9)	0.40
Previous hospitalisation	24 (44.4)	81 (39.7)	0.53
Previous antibiotic use	16 (29.6)	61 (29.9)	0.97
Duration of hospitalisation until 1st day of colistin treatment (days)	18.0 ± 15.3	18.4 ± 27.4	0.23
Duration of ICU stay until 1st day of colistin treatment (days)	10.3 ± 8.6	11.7 ± 13.0	0.37
Mechanical ventilation	43 (79.6)	155 (76.0)	0.57
<b>Special treatments</b>			
Blood transfusion	43 (79.6)	149 (73.0)	0.32
Steroid treatment	25 (46.3)	68 (33.3)	0.078
Haemodialysis	8 (14.8)	22 (10.8)	0.41
Growth factors	1 (1.9)	17 (8.3)	0.13
Anti-tumour therapy	7 (13.0)	14 (6.9)	0.16
Other	4 (7.4)	18 (8.8)	1.00
Urinary catheter	50 (92.6)	187 (91.7)	1.00

Tracheostomy	27 (50.0)	112 (54.9)	0.52
Bronchoscopy	9 (16.7)	20 (9.8)	0.16
Infection site			
Pneumonia	16 (29.6)	139 (68.1)	<0.001
Urinary tract	1 (1.9)	12 (5.9)	0.31
Abdominal	12 (22.2)	10 (4.9)	<0.001
Orthopaedic	0 (0)	2 (1.0)	1.00
Surgical	2 (3.7)	6 (2.9)	0.68
Skin/soft tissue	0 (0)	5 (2.5)	0.59
Bacteraemia	14 (25.9)	19 (9.3)	<0.001
Catheter	6 (11.1)	10 (4.9)	0.11
Cerebrospinal fluid	3 (5.6)	1 (0.5)	0.03
Responsible pathogen			
<i>Acinetobacter baumannii</i>	32 (59.3)	138 (67.6)	0.25
<i>Pseudomonas aeruginosa</i>	17 (31.5)	51 (25.0)	0.34
<i>Klebsiella pneumoniae</i>	5 (9.3)	13 (6.4)	0.55
Other	0 (0)	2 (1.0)	1.00
POS pathogen	30 (55.6)	106 (52.0)	0.63
Average daily dose of colistin (10 <sup>6</sup> IU/mL)	6.1 ± 2.5	6.2 ± 2.4	0.78
Duration of colistin administration (days)	18.1 ± 14.7	17.8 ± 11.1	0.35
Administered regimens			
Combination therapy	48 (88.9)	174 (85.3)	0.50
Colistin or colistin/meropenem regimen	33 (61.1)	165 (80.9)	0.002
Outcomes			
Nephrotoxicity	10/52 (19.2)	16/199 (8.0)	0.037
ΔCreatinine (creatinine at end – creatinine at start)	0.58 ± 1.48 mg/dL or 51.2 ± 130.8 μmol/L	0.06 ± 1.08 mg/dL or 5.3 ± 95.5 μmol/L	0.038
ΔCreatinine/creatinine at start	0.70 ± 1.31	0.15 ± 0.84	0.018

S.D., standard deviation; APACHE, Acute Physiology and Chronic Health Evaluation; ICU, Intensive Care Unit; POS, polymyxin-only-susceptible; IU, international units.

<sup>a</sup> Among urogenital co-morbidities were bladder cancer, renal disease, glomerulonephritis, kidney cancer and kidney stones.

<sup>b</sup> Among haematological co-morbidities were anaemia, bleeding diathesis, coagulation disorders, and haemopoietic and lymphoreticular malignancies.

<sup>c</sup> Among neurological co-morbidities were Alzheimer's disease, brain tumour, cerebral aneurysm, stroke and sclerosis.

**Table 2**

Outcome of infection due to different pathogens, according to the specific therapeutic regimen received

Pathogen	Infection outcome	Regimen					All regimens
		COL monotherapy <sup>a</sup>	COL + MER <sup>b</sup>	COL + PIP/TAZ	COL + SAM	COL + other agents <sup>a</sup>	
<i>Acinetobacter baumannii</i>	Cure [ <i>n/N</i> (%)]	20/23 (87.0) *	99/118 (83.9)	4/6 (67.7)	8/11 (72.7)	7/12 (58.3)	138/170 (81.2)
	Deterioration [ <i>n/N</i> (%)]	3/23 (13.0) *	19/118 (16.1)	2/6 (33.3)	3/11 (27.3)	5/12 (41.7)	32/170 (18.8)
<i>Pseudomonas aeruginosa</i>	Cure [ <i>n/N</i> (%)]	9/12 (75.0)	24/28 (85.7)	6/10 (60)	1/1	11/17 (64.7)	51/68 (75.0)
	Deterioration [ <i>n/N</i> (%)]	3/12 (25.0)	4/28 (14.3)	4/10 (40)	0/1	6/17 (25.3)	17/68 (25.0)
<i>Klebsiella pneumoniae</i>	Cure [ <i>n/N</i> (%)]	0	11/15 (73.3)	1/1	–	1/2	15/18 (83.3)
	Deterioration [ <i>n/N</i> (%)]	0	4/15 (26.7)	0/1	–	1/2	5/18 (27.8)
All pathogens	Cure [ <i>n/N</i> (%)]	30/36 (83.3) **	135/162 (83.3) ††	11/17 (64.7)	9/12 (75.0)	19/31 (61.3)	204/258 (79.1)
	Deterioration [ <i>n/N</i> (%)]	6/36 (16.7) **	27/162 (16.7) ††	6/17 (35.3)	3/12 (25.0)	12/31 (38.7)	54/258 (20.9)

COL, colistin; MER, meropenem; PIP/TAZ, piperacillin/tazobactam; SAM, ampicillin/sulbactam.

<sup>a</sup> Other agents included aminoglycosides (11 patients), imipenem (10 patients), cephalosporins (7 patients), aztreonam (2 patients) and

ciprofloxacin (1 patient).

<sup>a</sup> Statistically significant differences between groups of patients: COL monotherapy vs. COL + PIP/TAZ or COL + SAM or COL + other agents: \*  $P = 0.076$  (not significant) for infections caused by *A. baumannii*; \*\*  $P = 0.05$  for infections caused by all pathogens.

<sup>b</sup> Statistically significant differences between groups of patients: COL + MER vs. COL + PIP/TAZ or COL + SAM or COL + other agents: †  $P = 0.026$  for infections caused by *A. baumannii*; ††  $P = 0.003$  for infections caused by all pathogens.

Relative comparisons for infections caused by *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* were not meaningful because of the small number of cases.

**Table 3**

Backward multivariate logistic regression model for cure of infection (dependent variable) <sup>a</sup>

Variables in the equation	aOR	95% CIs for OR	P-value
COL or COL + MER treatment	3	1.3–7.1	0.01
Age (years)	0.96	0.94–0.99	0.04
Pneumonia	7.9	3.6–17.2	<0.001
Proportion of creatinine change <sup>b</sup>	0.69	0.49–0.96	0.029

aOR, adjusted odds ratio; CI, confidence interval; COL, colistin; MER, meropenem.

<sup>a</sup> Any variable that was significantly associated with cure of infection in the univariate analysis (Table 1) was entered in the backward multivariate logistic regression model. Six variables were removed from the equation (probability for stepwise removal was set at  $P > 0.05$ ): nephrotoxicity; central nervous system infection; bacteraemia; abdominal infection; Acute Physiology and Chronic Health Evaluation (APACHE) II score; and malignancy.

<sup>b</sup> (Creatinine at end of COL treatment – creatinine at start of COL treatment)/creatinine at start of COL treatment.