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INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Efficacy and Safety of Colistin in the Treatment of Infections Caused by Multidrug-resistant *Pseudomonas aeruginosa* in Patients with Hematologic Malignancy: A Matched Pair Analysis

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Abstract

Objective A rise in infections with multidrug-resistant *Pseudomonas aeruginosa* (MDR-PA) is a significant contributor to increased morbidity and mortality of patients with hematologic malignancies. The aim of this study was to determine the efficacy and safety of colistin (colistimethate sodium) in the treatment of serious infections caused by MDR-PA in these patients.

Patients and Methods A matched pair analysis of renal function, toxicities, and outcome of 26 patients receiving colistin and control subjects was done. All patients had clinical signs of sepsis; *P. aeruginosa* was isolated from blood in 69% of patients in colistin group and 84% in control group. Patients treated with colistin received 3 million units every 8 hours for a median duration of 13 days. Additionally, patients received at least two additional antimicrobial or antifungal drugs.

Results Resolution of infection was achieved in twenty patients (76.9%) receiving colistin and in 17 (65.4%) control subjects. Mortality rate was 11% in both groups. There was no statistically significant difference in the level of serum creatinine, creatinine clearance, or potassium levels before and after treatment between groups. Only one patient receiving colistin developed *de novo* renal failure and one displayed transient neurologic toxicity.

Conclusion Our results suggest that in patients with hematologic malignancies, colistin is effective in treating severe infections caused by MDR-PA while maintaining an acceptable toxicity profile. Prospective randomized studies comparing efficacy and safety of colistin with those of other antipseudomonal drugs are needed.

Key words: colistin, MDR bacteria, neutropenia, neutropenic fever

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Introduction

The emergence of infections caused by multidrug-resistant (MDR) gram-negative bacteria, coupled with the lack of new agents effective against resistant strains (1), has resulted in the reconsideration of old and almost forgotten agents, such as colistin. Colistin, or polymyxin E, is a polypeptide antibiotic, a member of family of polymyxins. Intravenous formulations were abandoned in the early 1980's for two reasons: reports of high nephrotoxicity and neurotoxicity and the development of second- and third-generation cephalosporins. Since then, use of colistin has been restricted to the therapy of severe pulmonary infections in patients with cystic fibrosis. Colistin is available as colistin sulfate, a form poorly absorbed from gastrointestinal tract used in topical preparations and for intestinal decontamination, and colistimethate sodium, used intravenously and intramuscularly. Both colistin sulfate and colistimethate can be administered by inhalation.

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Colistin was shown to have retained activity against contemporary isolates of many gram-negative species, such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Klebsiella pneumoniae* (2), although *Proteus* spp., *Providencia* spp., and *Serratia* spp. are usually resistant to colistin. Polymyxins have exhibited a synergistic effect against Gram-negative organisms in combination with a number of other antimicrobials such as tetracyclines, chloramphenicol and beta-lactams. Early in its clinical utilization, colistin was associated with significant nephrotoxicity, with rates of up to 20.2% and 36% in general population and patient with pre-existing renal disease, respectively (3). However, recent studies have shown lower incidence of renal toxicity (4), with one study reporting nephrotoxicity not greater than one associated with ampicillin/sulbactam use (5).

Due to the widespread use of broad-spectrum antibiotic agents in patients with hematologic malignancies, a frequent selection of multi-drug resistant bacteria occurs. Recently, efficacy and safety of colistin were evaluated in patients primarily treated for severe ventilator-associated pneumonia in the setting of intensive care units (4-7), while only one report addressed the population of neutropenic patients: Hachem et al evaluated the efficacy of colistin in cancer patients, mostly patients with hematological malignancy, and found it to be as effective and safe as beta-lactams or fluoroquinolones in the treatment of infections caused by MDR *Pseudomonas aeruginosa* (MDR-PA) (8).

In order to better define the role of colistin in the treatment of MDR-PA infections in patients with hematologic malignancies, and to further evaluate safety and efficacy of the drug in this particular subset of patients, we compared markers of renal function in two groups of patients treated in our center: those receiving intravenous colistin for isolated MDR-PA and those in whom susceptible *P. aeruginosa* was isolated and appropriate antibiotic administered.

Patients and Methods

Patient selection

This is a retrospective, 1:1 matched, case-control study, conducted at the Division of Hematology at Clinical Hospital Center, Zagreb, Croatia. Microbiology laboratory database and pharmacy requisition logs were used to identify patients that received intravenous colistin (colistimethate sodium) for infection caused by MDR-PA on an inpatient basis between February 2002 and December 2006. A total of 26 patients were included and for each patient representing a case, a patient serving as a control was identified among patients in whom the isolated *P. aeruginosa* strain was susceptible to at least one antipseudomonal agent other than colistin and who were treated accordingly. Matching was designed in a stepwise manner for two criteria, the first referring to the site of isolation, and the second focusing on the demographic details (age, gender, underlying disease and type of treatment received for hematological malignancy). All selected patients had clinical signs of sepsis. The following variables were recorded: age, gender, primary disease, height, weight, treatment received, disease status at the beginning of treatment, site of infection, length and dosage of colistin therapy, simultaneous use of other antibiotics (including duration and dosage), clinical and microbiological response, and mortality during the episode of infection.

Data collection

Clinical and demographic data were collected from patients' records, pharmacy and laboratory databases at the Clinical Hospital Center Zagreb. Creatinine, urea and potassium values at the beginning, during, and at the end of colistin treatment were recorded.

Dosing of colistin

Patients were treated with colistimethate sodium (Grünenthal, Stolberg) administered intravenously. The usual dose administered was 3 million units (MU) every 8 hours (1 MU equals 79 mg; on average patients received 3.2 mg/kg). In case of renal impairment dosage was reduced as reported previously (for the serum creatinine of 105-140 μmol/L, dose of 2.5-3.8 mg/kg/12 h was administered; for creatinine of 141-220 μmol/L, 2 mg/kg/24 h were given; for creatinine above 221 μmol/L, dose was 1.5 mg/kg/48 h) (6). Patients included in the control group received antibiotic therapy according to the susceptibility of *P. aeruginosa* (cefepime, meropenem, or piperacillin/tazobactam), administered at usual doses, as per recommendations included in the package insert.

Definitions

The site of infection was determined based on the clinical signs and symptoms of individual patients, imaging results, and the isolation of *P. aeruginosa* from clinical specimens collected. The severity of clinical condition was assessed according to the American College of Chest Physicians Consensus Committee as follows: sepsis, severe sepsis, septic shock and multiorgan failure (MOF) (9). White blood cell count criterion for sepsis was not used due to our patients' primary disease and the therapy they underwent. The clinical response was rated as (i) clinical response at the end of therapy, if there was resolution of fever and signs and symptoms of infection; (ii) failure, in the absence of resolution or worsening of the signs and symptoms of infection. MDR-PA strains were defined as resistant to all antibiotic agents routinely tested, including penicillins, aminoglycosides, ampicillin/sulbactam, cephalosporins, aztreonam, carbapenems, fluoroquinolones, tetracyclines, and susceptible only to colistin. Patients were followed until the end of treatment for outcome and adverse events. Renal failure was defined as serum creatinine concentration >150 μmol/L, or as an increase of $\geq$50% from the baseline value in patients with preexisting renal impairment. Neutropenia was defined as an absolute neutrophil count of $\leq 0.5\times10^{9}$/L.

Table 1. Patient Characteristics

	Colistin	Control
Sex		
male	12 (46%)	15 (58%)
female	14 (54%)	11 (42%)
Age		
average	35	37
range	17-60	18-63
Underlying disease		
Acute myeloid leukemia	15 (57%)	15 (57%)
Acute lymphoblastic leukemia	3 (12%)	2 (8%)
Non-Hodgkin lymphoma	4 (15%)	2 (8%)
Multiple myeloma	1 (4%)	4 (15%)
Aplastic anemia	2 (8%)	1 (4%)
Chronic myeloid leukemia	1 (4%)	0
Hodgkin's disease	0	2 (8%)
Therapy received		
chemotherapy	11 (42%)	12 (46%)
autologous BMT*	7 (27%)	9 (35%)
allogeneic BMT	7 (27%)	3 (12%)
no therapy	1 (4%)	2 (8%)
P. aeruginosa isolation site		
blood cultures	22 (84%)	18 (69%)
skin lesions	3 (12%)	7 (27%)
sputum	1 (4%)	1 (4%)
Sepsis characteristics		
sepsis	12 (46%)	14 (53%)
severe sepsis	10 (39%)	9 (35%)
septic shock	4 (15%)	3 (12%)
multiorgan failure	0	0
Antipseudomonal therapy profile		
monotherapy	3 (12%)	4 (15%)
dual therapy	11 (42%)	22 (85%)
triple therapy	12 (46%)	0

* BMT – bone marrow transplantation

Statistical analysis

Categorical variables were expressed as percentages and continuous variables as mean ± standard deviation. To determine statistical significance t-test for independent samples and chi-squared test, where applicable, were used.

Results

Patient characteristics

During study period 26 patients were treated with intravenously administered colistin; 26 case-matched control subjects were chosen. The *P. aeruginosa* strains isolated from the control subjects were susceptible to at least one drug other than colistin, and thus, were treated with one of three other antipseudomonal drugs usually used as first-line therapy in our institution (cefepime, piperacillin/tazobactam, or meropenem), according to the susceptibility profile. Details on age, sex, underlying disease, therapy received, sepsis classification, and concomitant therapy are shown in Table 1. All patients, except one in the colistin group and two in the control group, were neutropenic at the time of infection. Patients in the colistin group were treated for a median duration of 13 (range 3-23) days. Due to the nature of their primary condition and severity of infection, most patients received simultaneously more than one antipseudomonal drug and additional antimicrobial drugs (Table 1 and Fig. 1).

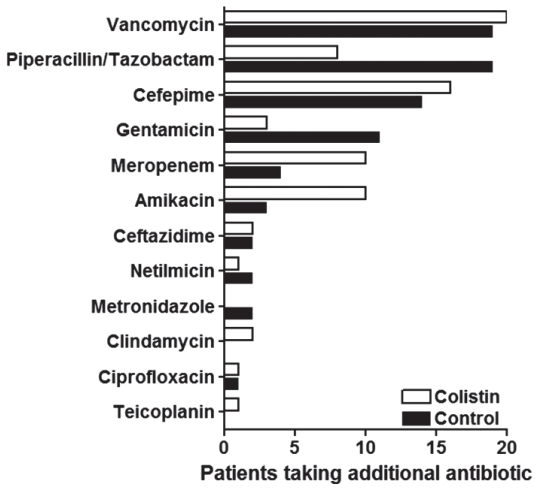

Figure 1. Additional antibiotics used in study patients.

Efficacy

As depicted in Table 2, in 20 (76.9%) patients receiving colistin and 17 (65.4%) patients in the control group infection resolved with therapy. In the colistin group, out of 6 patients that failed therapy, three died from an uncontrolled infection, two did not respond to colistin, but did respond to the subsequently used antipseudomonal drug, and one developed an allergic reaction prompting therapy discontinuation. We observed no statistically significant difference in efficacy between group receiving colistin and control group. Furthermore, there was no difference in mortality: three patients (11%) in both groups died as a consequence of uncontrolled infection and MOF. Only the difference in number of antipseudomonal drugs administered was statistically significant between the colistin and control groups in an analysis evaluating effect of age, type of disease, type of treatment, sepsis characteristics, and number of antipseudomonal drugs administered on treatment outcome.

Safety

Renal failure was observed in 3 patients (11%) in the colistin group and in none of control patients (p=0.0744); of note, two of three patients who developed renal failure had pre-existing renal impairment. One of these patients quickly developed MOF and died after only 3 days of therapy. The other two patients received reduced doses of colistin and completed therapy with favorable outcome. In another patient creatinine level at the start of colistin therapy was 436 mmol/L; and with continuous venovenous hemofiltration he was able to complete colistin therapy with favorable outcome and complete restoration of renal function. There was no statistically significant difference between the groups re-

Table 2. Colistin Efficacy

	Colistin n = 26	Control n = 26	p value
Overall	20/26	17/26	0.5404
Age group			
< 50	17/22	11/17	0.2505
≥ 50	3/4	6/9	
Disease			
acute leukemia	16/18	11/16	0.4597
other*	4/8	6/10	
Disease state			
active	11/14	10/13	0.8889
remission	9/12	7/13	0.1444
Treatment			
chemotherapy/immunotherapy	10/12	10/14	0.3464
BMT**	10/14	7/12	0.7379
Sepsis classification			
sepsis	9/12	10/14	0.5482
severe sepsis/septic shock	11/14	7/12	0.1250
Microbiological identification			
bacteremia	10/13	8/10	0.8707
non-bacteremia	10/13	9/16	0.1286
Antipseudomonal drugs used			
≤ 2	5/6	14/20	0.476
> 2	15/20	3/6	0.2446

*includes multiple myeloma, aplastic anemia, Hodgkin's disease, Non Hodgkin's lymphoma

** BMT – bone marrow transplantation

garding the level of serum creatinine or potassium before and after treatment (Fig. 2B, C). However, we did notice a rise in urea levels after the treatment with colistin (Fig. 2A). In the colistin group 5 patients had urea values above 15 mmol/L. One of the patients had approximately the same value prior to colistin therapy, and other two patients died from uncontrolled sepsis and resulting MOF. Of note, however, is that colistin recipients received potential nephrotoxic medications (defined as ones with incidence of renal failure of ≥1%) more often than the patients in the control group, a difference that was statistically significant ($p<0.05$).

Only one patient displayed signs of neurological toxicity, Jackson's partial epilepsy with a secondary generalization. We continued administering colistin at a reduced dose and seizure activity subsequently ceased. In one other patient colistin was discontinued due to a suspected allergic reaction. No other adverse events were noted.

Discussion

This study suggests that colistin is a viable alternative to other antibiotics used for treating life-threatening infections caused by MDR-PA in patients with hematologic malignancies. It is the second of only two retrospective analyses in this particular population of patients, and the one with the largest cohort of neutropenic patients, exploring the efficacy and safety of colistin. Of 26 patients treated with colistin, 20 (77%) had achieved clinical response prompting drug discontinuation. As shown in Table 2, three of those patients presented with septic shock, a finding that further validates the hypothesis of colistin's efficacy in this group of patients. Furthermore, colistin proved to be a safe drug in our group of patients, given the low incidence of renal failure (11%) that did not differ from the one observed in the control group. Finally, our study affirmed the recently published data on colistin safety, however, also extended it to the group of patients that were not previously evaluated (4, 5). We did notice a statistically significant rise in urea level post-therapy in the colistin group when compared to the control group. A possible cause could include colistin effect; however, the rise could also be attributed to the renal impairment in the setting of MOF due to uncontrolled infection (two out of five patients with observed rise in urea level died of MOF). Only one patient showed signs of neurologic toxicity; however, given a severe, life threatening infection, colistin was dose reduced and continued without neurologic sequelae. In our series of patients colistin exhibited an acceptable level of toxicity, especially considering the severity of the infections in neutropenic patients caused by a multidrug resistant agent.

Although *P. aeruginosa* isolated from the present patients was susceptible only to colistin, many patients received more than one antipseudomonal drug, in the majority of cases an antipseudomonal cephalosporin. There was a statistically higher number of concomitant antipseudomonal agents used in the colistin group. While one could speculate that this contributed to the clinical response rate in colistin recipients, given culture and susceptibility data showing *P. aeruginosa* highly resistant to all agents except colistin, that scenario is unlikely. To that end, the higher number of concomitant antipseudomonal agents used in colistin recipients likely reflects the gravity of patients' clinical condition and the frequently employed approach to treating MDR bacterial infections, where in vitro susceptibility data do not necessarily reflect in vivo sensitivities (10). Also, since this is a retrospective analysis and different antipseudomonal agents were simultaneously administered in various combinations, it was not possible to analyze the influence of certain combination on response rate and survival. Therefore, we cannot make a firm conclusion or recommendation as to which agent should be used in combination with colistin.

There are several limitations to this study. First, the number of patients included is quite small despite the fact that the study period spanned almost 5 years. This is multifactorial in nature and is reflective of measures undertaken by Infectious Disease Control Unit and Department of Microbiology to curb further spread of the resistant strain, as well as scarcity of MDR-PA infections in patients with hematologic malignancies. Also, this study is retrospective; however, in order to conduct a randomized prospective trial, the trial drug should be established to be at least as effective as the standard therapy. In this particular population of patients,

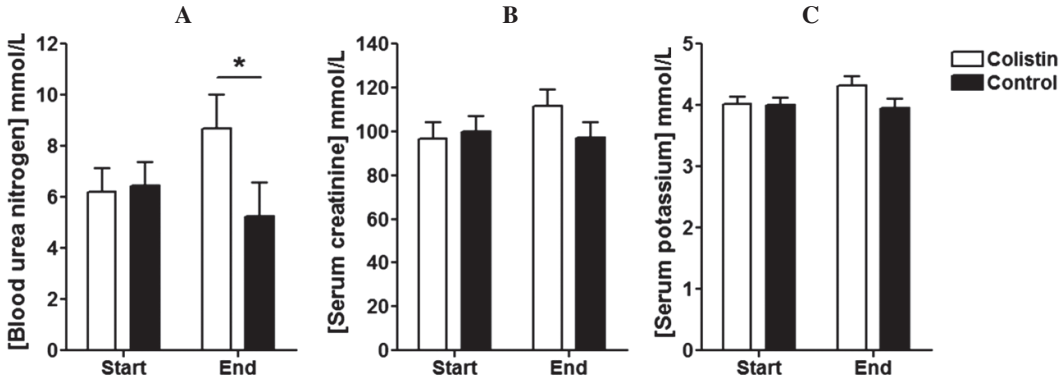

Figure 2. **Safety of colistin use. Levels of blood urea nitrogen (A), serum creatinine (B), and potassium (C) at the initiation and upon completion of treatment. *indicates p<0.01**

randomized trials examining antibiotic treatment, especially as monotherapy, are sparse, if any. In addition, the paucity of studies dealing with MDR infections in patients with hematologic malignancies underscores the need and interest in studies such as the present study. To that end, data presented here contribute significantly to increasing knowledge about possibilities and potential risks of intravenous colistin use in immunocompromised, neutropenic patients.

In conclusion, colistin is a safe and effective drug when used to treat MDR-PA infections in patients with hematologic malignancies; however, further prospective randomized control trials are needed to establish its role in the treatment of complicated MDR-PA infections. While a randomized trial would be unethical in a patient population such as ours, as it would result in a denial of an only possible life saving antibiotic, alternate clinical scenarios, similar to the one described by Hachem et al (8), should be used to compare efficacy and safety of colistin, both as monotherapy and in combination with other antipseudomonal drugs, to the currently established therapies. Until such studies are designed and conducted, colistin should be used with caution, primarily to avoid selection of resistant strains, as the drug is often the only treatment option when MDR strains emerge.

The authors state that they have no Conflict of Interest (COI).

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