Research

Intravenous colistin in the treatment of sepsis from multiresistant Gram-negative bacilli in critically ill patients

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Abstract

Introduction The increasing prevalence of multiresistant Gram-negative strains in intensive care units (ICUs) has recently rekindled interest in colistin, a bactericidal antibiotic that was used in the 1960s for treatment of infections caused by Gram-negative bacilli. We conducted the present observational study to evaluate the efficacy of intravenous colistin in the treatment of critically ill patients with sepsis caused by Gram-negative bacilli resistant to all other antibiotics.

Patients and method Critically ill patients with sepsis caused by Gram-negative bacilli resistant to all antibiotics with the exception of colistin were treated in the six-bed ICU of a trauma hospital. Diagnosis of infection was based on clinical data and isolation of bacteria, and the bacteria were tested with respect to their susceptibility to colistin. Clinical response to colistin was evaluated.

Results Twenty-four patients (mean age 44.3 years, mean Acute Physiology and Chronic Health Evaluation II score 20.6) received 26 courses of colistin. Clinical response was observed for 73% of the treatments. Survival at 30 days was 57.7%. Deterioration in renal function was observed in 14.3% of 21 patients who were not already receiving renal replacement therapy, but in only one case did this deterioration have serious clinical consequences.

Conclusion The lack of a control group in the present study does not allow any definite conclusions to be drawn regarding the clinical effectiveness of colistin. On the other hand, this drug has an acceptable safety profile and its use should be considered in severe infections with multiresistant Gram-negative bacilli.

Keywords *Acinetobacter baumannii*, colistin, intensive care unit, *Pseudomonas aeruginosa*, sepsis

Introduction

Infections with resistant organisms represent a serious menace in critically ill patients. As options for effective chemotherapy diminish, intensive care unit (ICU) mortality will increase. Mortality rates as high as 60% have been reported for serious infections (ventilator-associated pneumonia [VAP], bloodstream infections) with inappropriate initial treatment [1–6]. In a recent study [7], inadequate antimicrobial treatment of infection was an important and independent determinant of mortality in critically ill patients. In that series patients receiving inadequate treatment had an in-hospital mortality rate of 52.1%, as compared with 12.2% in those patients who were adequately treated.

APACHE = Acute Physiology and Chronic Health Evaluation; CVVHD = continuous venovenous hemodiafiltration; ICU = intensive care unit; VAP = ventilator-associated pneumonia.

The increasing prevalence of multiresistant Gram-negative strains in ICUs has recently rekindled interest in colistin [8–12], a bactericidal antibiotic that was used in the 1960s for treatment of infections caused by Gram-negative bacilli. A high incidence of adverse effects (nephrotoxicity, neurotoxicity), along with the development of newer effective drugs with better safety profiles, resulted in the practical abandonment of systemic use of colistin, although it still remains active *in vitro* against practically all strains of *Pseudomonas aeruginosa* and *Acinetobacter* spp. The presence of multiresistant *P. aeruginosa* and *Acinetobacter baumannii* strains in our ICU prompted us to try treatment with colistin as a last resort in patients with serious infections with such strains. Here we report 3 years of experience with intravenous colistin in the treatment of Gram-negative sepsis.

Patients and method

We studied critically ill patients with sepsis caused by Gram-negative bacilli resistant to all antibiotics with the exception of colistin. The patients were treated in a six-bed ICU in a trauma hospital.

Diagnosis of infection was based on clinical data and the isolation of bacteria, either from a normally sterile site or from quantitative cultures of tracheal aspirate or bronchoalveolar lavage. More specifically, the clinical prerequisites for the diagnosis of VAP were as follows: presence of at least two of fever (>38.3°C), leukocytosis or leukopenia, and purulent bronchial secretions; and a new and persistent infiltrate on chest radiography. On isolation of strains of *P. aeruginosa* and *A. baumannii* that were resistant to all antibiotics apart from colistin, intravenous colistin sulfomethate sodium (Colistin; Norma, Athens, Greece) was initiated at the discretion of the attending physician. The dosage of colistin, administered intravenously, was 3 MU three times daily, adjusted for creatinine clearance [10].

Susceptibility testing was done using an automated broth microdilution test (Vitek; bioMérieux, Durham, NC, USA). The breakpoints for susceptibility were those recommended by the National Committee for Clinical Laboratory Standards. Susceptibility to colistin was tested using the disk diffusion method, with a 10 µg colistin disk (Oxoid Ltd, Basingstoke, Hants, UK). Isolated bacilli were considered susceptible if the inhibition zone was 11 mm or greater.

Results

In all, 28 patients were treated with colistin. In 16 cases colistin was part of the initial empiric regimen based on previous surveillance cultures, with subsequent cultures confirming the sensitivity pattern. For the remaining patients, colistin was introduced when culture results became available in those who had not responded to the initial empiric regimen. Four of the 28 patients died within 48 hours of the initiation of colistin; these patients were not included in the analysis because they were not considered true therapeutic failures. Data on the remaining 24 patients are presented in Table 1. The mean age of the patients was 44.3 years and the mean Acute Physiology and Chronic Health Evaluation (APACHE) II score was 20.6. In five patients multiple organ failure was present at the initiation of colistin. A total of 26 courses of colistin were given, for the following infections: VAP (15 cases), empyema thoracis (one case), post-traumatic meningitis (one case), sinusitis (one case), urinary tract infection (one case), catheter-related sepsis (three cases), and sepsis of unknown primary origin (four cases). The offending pathogen was *P. aeruginosa* in 20 cases and *A. baumannii* in six. In six cases a co-pathogen was isolated. Median duration of treatment with colistin was 13.5 days (range 4–24 days). In all cases a second antibiotic (ceftazidime in 16, piperacillin/tazobactam in six, and a carbapenem in four cases) was added to the therapeutic regimen, despite documented resistance.

Clinical response, judged as abatement of fever for at least 48 hours with parallel improvement in vital signs, was observed for 17 of the 26 treatments. In two patients with septic shock (one hypothermic and the other with low-grade fever) it was possible to stop vasopressors in the following 48 hours, and this was also considered proof of response. Thus, clinical response was seen for 19 out of 26 treatments with colistin (73%). Survival at 30 days was 57.7%.

In the subgroup of patients with bacteremia (11 patients), an initial clinical response to colistin was observed in seven patients and the ICU mortality was 54.5%. Additional blood culture data after initiation of colistin were available in two of the clinical responders, and bacterial eradication was confirmed in both. In the subgroup of patients with VAP, 11 out of 15 patients (73.3%) had an initial clinical response to colistin, bacterial eradication was observed in eight (53.3%), and ICU mortality was 40%.

Three patients had already developed acute renal failure at the initiation of treatment with colistin and were being treated with continuous venovenous hemodiafiltration (CVVHD). None of them survived. The other patients had a serum creatinine below 2.5 mg/dl with one exception (a patient with serum creatinine 3.2 mg/dl), and all had adequate diuresis. Only patients 8, 17 and 24 (14.3%) had an increase in serum creatinine of greater than 1 mg/dl during treatment, with no serious consequences in patients 8 and 17. Only patient 24 developed anuria and serious impairment in renal function requiring CVVHD (Table 2).

No patient developed clinically apparent neuromuscular transmission blockade.

Discussion

Colistin is a cationic polypeptide antibiotic of the polymyxin family that is rapidly bactericidal to Gram-negative bacteria. The action of colistin is by a detergent-like mechanism, interfering with the structure and function of the outer cytoplasmic

Table 1

Critically ill patients treated with colistin: clinical characteristics and outcome

Patient	Age (years)	Sex	APACHE II score	Underlying disease	Infection	Pathogen	Response, outcome
1	34	M	21	Trauma, ARDS	VAP	*P. aeruginosa*	Initial response, Death
2	22	M	17	Trauma	VAP	*P. aeruginosa*	Response
3	27	M	14	Trauma	VAP	*P. aeruginosa*	Response
4	36	F	23	Burns, MOF (three organs)	VAP	*P. aeruginosa*	No response, death
5	25	F	22	Trauma, ARDS	VAP	*P. aeruginosa*	No response, death
6	47	M	13	Trauma	VAP	*P. aeruginosa*	Response
7	64	M	17	Trauma	VAP	*P. aeruginosa*	Response
8	52	F	16	Trauma	VAP	*P. aeruginosa*	Response
9	29	M	26	Pancreatitis, MOF (three organs)	VAP	*P. aeruginosa*	Initial response, death
10	38	M	14	Subarachnoid hemorrhage	VAP	*P. aeruginosa*	Response
11	66	M	28	Head and neck cancer, surgery, MOF (three organs)	VAP	*P. aeruginosa*	No response, death
12	34	F	16	Trauma	VAP	*Acinetobacter* spp.	Response
13	80	M	21	Sternotomy, ARDS	VAP	*Acinetobacter* spp.	Response
14	43	M	19	Trauma	VAP	*Acinetobacter* spp.	Response
15	28	F	24	Morbid obesity, bowel resection	VAP	*Acinetobacter* spp.	No response, death
16	20	F	17	Trauma	Post-traumatic meningitis	*Acinetobacter* spp.	Response
					Sinusitis	*P. aeruginosa*	
					Urosepsis	*P. aeruginosa*	
17	61	M	20	Trauma	Catheter-related sepsis	*P. aeruginosa*	Response
18	35	M	14	Trauma	Catheter-related sepsis	*P. aeruginosa*	Response
19	62	M	29	Trauma, MOF (two organs), CVVHD	Catheter -related sepsis	*P. aeruginosa*	No response, death
20	64	F	28	Burns, MOF (two organs), CVVHD	Sepsis of unknown primary origin	*P. aeruginosa*	No response, death
21	73	M	32	Cancer of the colon, bowel resection, MOF (four organs)	Sepsis of unknown primary origin	*P. aeruginosa*	Initial response, death
22	29	M	14	Trauma	Sepsis of unknown primary origin	*P. aeruginosa*	Response
23	20	M	22	Trauma, crush syndrome, CVVHD	Empyema thoracis	*P. aeruginosa*	No response, death
24	74	M	28	Aneurysm of the abdominal aorta, elective operation	Sepsis of unknown primary origin	*Acinetobacter* spp.	Initial response, death

F, female; M, male; MOF, multiple organ failure; CVVHD, continuous venovenous hemodiafiltration.

membrane of bacteria and resulting in bacterial death [11,13]. It is administered as colistin sulfomethate sodium and its hydrolysis releases the active drug. It is removed by glomerular filtration [10].

Colistin remains active *in vitro* against almost all strains of *P. aeruginosa*, *Klebsiella pneumoniae*, *Acinetobacter* spp., and *Enterobacter* spp. On the other hand, *Proteus* spp., *Providencia* spp., *Serratia* spp., *Burkholderia cepacia*, and some

Table 2

Characteristics of patients with impairment in renal function after initiation of colistin

Patient	Characteristics	Serum creatinine (mg/dl)		
		Cr1	Cr2	Cr3
8	Age 52 years, female, trauma, VAP, septic shock	0.9	2.1	1.4
17	Age 61 years, male, trauma, catheter-related sepsis, diabetes mellitus	1.1	2.3	1.5
24	Age 74 years, male, aneurysm of the abdominal aorta, elective operation. Sepsis of unknown primary origin, previous myocardial infarction, hypertension	2.4	5.1	CVVHD, death

Cr1, serum creatinine at initiation of colistin; Cr2, highest value of creatinine during treatment with colistin; Cr3, serum creatinine 7 days after completion of treatment with colistin; CVVHD, continuous venovenous hemodiafiltration; VAP, ventilator-associated pneumonia.

strains of *Stenotrophomonas maltophilia* are usually resistant to colistin [8–18]. Cross-resistance with other antibiotics has not been reported [10,13], and acquired resistance is rare [11,17]. Although lower susceptibility rates for *P. aeruginosa* have been reported in patients with cystic fibrosis undergoing chronic prophylactic treatment with inhaled colistin [18], 81% of strains of *P. aeruginosa* from such patients are still susceptible to colistin [14].

With regard to clinical efficacy, data are limited. In the 1960s the drug, administered mostly via the intramuscular route, was found to be of use in the treatment of infections with Gram-negative bacteria resistant to other antibiotics. Response was better in patients with bloodstream infections resulting from urinary tract infection. Colistin was less effective in patients with osteomyelitis, biliary tract disease, endocarditis, and suppurative infections of the lung (probably because of suboptimal concentrations locally), and it was ineffective in the treatment of Gram-negative infections in neutropenic patients [10,11,13].

In recent years intravenous colistin has occasionally been used in acute exacerbations of multiresistant *P. aeruginosa* in patients with cystic fibrosis [19–21]. With regard to adult patients without cystic fibrosis treated with colistin, an observational study [9] reported a clinical response rate of 58%. In that study the drug was used in 59 patients with serious infections with *A. baumannii* (65%) and *P. aeruginosa* (35%) resistant to all other antibiotics. Of the patients studied, 65% were critically ill and the mean APACHE II score was 13.1. Response was suboptimal (25%) in patients with pneumonia. Recently, Garnacho-Montero and coworkers [12] reported the only controlled study of colistin in patients without cystic fibrosis. Patients with VAP caused by *A. baumannii* were treated with imipenem (21 patients) or, in the case of resistance to all other antibiotics, with colistin (14 patients). APACHE II scores at presentation and Sequential Organ Failure Assessment scores at the time of diagnosis of VAP were similar between the groups. Achieving clinical cure in 57% of cases, intravenous colistin was as effective as imipenem. No significant difference was observed between the two groups in terms of crude mortality, VAP attributed

mortality, microbiologic cure, or duration of ICU stay. Limitations of that study are the small number of patients included, open design, and lack of randomization.

Clinical response in the present study was somewhat better than in the study conducted by Levin and coworkers [9], despite a higher mean APACHE II score. The observed 30-day mortality rate of 42.3% in the present study is certainly high but not unexpectedly so for the severity of illness. Because mortality rates in the region of 50–60% have been reported in critically ill patients receiving inappropriate treatment [1–7], the use of colistin may indeed have been of clinical benefit in our patients.

Both the study by Levin and coworkers [9] and a study of an experimental pneumonia model with *Acinetobacter* sp. in immunocompetent mice [22] suggest that, despite good *in vitro* activity, the clinical efficacy of colistin may be suboptimal in Gram-negative pneumonia. On the other hand, Garnacho-Montero and coworkers [12] reported that colistin was not inferior to the standard treatment for VAP caused by *A. baumannii*, with a clinical cure rate of 57%. Results were rather better in our patients with VAP, in whom a clinical response was seen in 73.3% and bacterial eradication in 53.3%. Perhaps the high doses of colistin used in our study were in part responsible for this.

The dosage of colistin used in our study was more than double that usually recommended [9,10,12], although much higher doses – with a parallel increase in nephrotoxicity – have been reported in the past [23]. We opted for the higher dose because of the severity of the infections being treated. A recent study that reported that colistin methanosulfate is less rapidly bactericidal than is colistin in *P. aeruginosa* [14] offers retrospective justification for the higher dosage used in our ICU. It appears that peak concentrations of colistin methanosulfate 16 times the minimum inhibitory concentration or greater are required for complete *in vitro* killing of *P. aeruginosa* within 24 hours [14].

In the present study all patients received a β-lactam in addition to colistin, despite documented resistance. In some

cases the second drug was added to act against isolated co-pathogens, but in most patients this addition indicated the attending physician's lack of confidence in monotherapy with colistin. Although combinations of colistin with β-lactams are reported to be of unproven benefit [24,25], a recent study conducted in an *in vitro* pharmacodynamic model [28] reported synergy with ceftazidime for *P. aeruginosa* sensitive to colistin but resistant to other antibiotics, including ceftazidime. Synergy with colistin has been reported for trimethoprim–sulfamathoxazole (co-trimoxazole) [27] and rifampicin [26], but no patient in our study received these antibiotics.

A possible drawback of the present study is the use of the disk diffusion method for testing *in vitro* susceptibility to colistin. According to a recent study [15], this approach some-times yields falsely susceptible results. However, because errors are observed mainly for *S. maltophilia* and much less often for *Acinetobacter* spp., it appears unlikely that the use of a different method of susceptibility testing would materially influence our findings.

Toxicity, particularly nephrotoxicity, is an important concern with colistin. In the study conducted by Koch-Weser and coworkers [29], impairment in renal function – usually reversible with termination of treatment – was observed in 20.2% of 288 patients. Levin and coworkers [9] also reported a high incidence of nephrotoxicity (37%), especially in patients who already had compromised renal function [9]. Because most of the patients in both studies were seriously ill, it is highly probable that at least part of the reported toxicity was the result not of the drug but of the disease. On the other hand, experience with the drug in patients with cystic fibrosis, has shown only minimal nephrotoxicity [19–21,30]. Garnacho-Montero and coworkers [12], in patients with VAP, observed that there was no significant difference in development of renal failure between colistin and imipenem. In our study, despite a dosage of colistin that was much higher than that usually reported, nephrotoxicity was moderate (14.3%) and it is unlikely that this had a clinically significant impact in most cases, although the drug might have contributed to the poor outcome of patients under CVVHD.

Neurotoxicity and neuromuscular blockade were also reported with colistin in the 1960s [29,31], but more recent studies did not report clinically evident [9,30] or neurophysio-logic [12] abnormalities. No clinical neurotoxicity was observed in the present study.

Conclusion

Although our findings with colistin can be considered encour-aging in comparison with previous experience, the small number of patients, the concomitant use of β-lactams, and the absence of a control group in the study do not allow for a clear verdict on the clinical effectiveness of colistin. On the other hand, the moderate incidence of complications sug-

gests that colistin may be a relatively safe choice in patients with normal renal function, at least when administered in an ICU with proper monitoring of variables that affect renal func-tion. Pending a randomized controlled trial, the use of intra-venous colistin should be considered in severe infections with Gram-negative bacilli when it remains the only antibiotic to which the causative pathogen is sensitive *in vitro*.

Competing interests

None declared.

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