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Short Communication

Use of colistin in adult patients: A cross-sectional study

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ABSTRACT

Objectives: The aim of this study was to assess colistin use in a country endemic for multidrug-resistant Gram-negative bacteria (MDR-GNB).
Methods: Colistin prescription patterns were evaluated in 22 Italian centres. Factors associated with use of colistin in combination with other anti-MDR-GNB agents were also assessed.
Results: A total of 221 adults receiving colistin were included in the study. Their median age was 64 years (interquartile range 52–73 years) and 134 (61%) were male. Colistin was mostly administered intravenously (203/221; 92%) and mainly for targeted therapy (168/221; 76%). The most frequent indications for colistin therapy were bloodstream infection and lower respiratory tract infection. Intravenous colistin was administered in combination with at least another anti-MDR-GNB agent in 80% of cases (163/203). A loading dose of 9 MU of colistimethate was administered in 79% of patients receiving i.v. colistin and adequate maintenance doses in 85%. In multivariable analysis, empirical therapy [odds ratio (OR) = 3.25, 95% confidence interval (CI) 1.24–8.53; $P = 0.017$] and targeted therapy for carbapenem-resistant Enterobacterales infection (OR = 4.76, 95% CI 1.69–13.43; $P = 0.003$) were associated with use of colistin in combination with other agents, whilst chronic renal failure (OR = 0.39, 95% CI 0.17–0.88; $P = 0.024$) was associated with use of colistin monotherapy.
Conclusion: Colistin remains an important option for severe MDR-GNB infections when other treatments are not available. Despite inherent difficulties in optimising its use owing to peculiar pharmacokinetic/pharmacodynamic characteristics, colistin was mostly used appropriately in a country endemic for MDR-GNB.

1. Introduction

Colistin, a polymyxin antibiotic, is a last-resort treatment option for multidrug-resistant Gram-negative bacteria (MDR-GNB), especially carbapenem-resistant Enterobacterales (CRE) and non-fermenters [1–3].

Despite the fact that a reduction in its use will likely be observed in the near future owing to the recent marketing of several novel agents, colistin still remains among the few potentially active treatment options for carbapenem-resistant *Acinetobacter baumannii* (CRAB) and for other MDR-GNB resistant to novel compounds [1,2,4–6]. Very importantly, use of colistin should be reserved for these indications and should be avoided in the presence of dependable alternatives, since its effectiveness and safety can be impaired by several factors, including: (i) narrow therapeutic index, which may result in either suboptimal concentrations or nephrotoxicity [7]; (ii) suboptimal concentrations in lung tissue [8]; (iii) frequent unavailability of colistin therapeutic drug monitoring outside of research laboratories; and (iv) unintended treatment of colistin-resistant infections owing to possible limitations of some classical susceptibility testing methods [9]. Therefore, using colistin appropriately (e.g. correct indication, correct dosage, reserving it for infections caused by, or strongly suspected to be caused by, MDR-GNB) is certainly difficult but is of paramount importance for improving patient outcomes and relieving selective pressure due to suboptimal dosages on those strains for which colistin remains, or may remain, the only active therapeutic option.

Although several studies evaluating the use of colistin for selected MDR-GNB infections have been conducted over the last decades [3,6,10,11], little is known about the overall characteristics of colistin use in countries endemic for MDR-GNB. In light of this, assessing colistin prescription patterns is a fundamental step for ultimately tailoring antimicrobial stewardship interventions in order both to optimise colistin use and to preserve its activity in the long-term. In this cross-sectional study, prescription patterns of colistin in adult patients in Italy, a country endemic for MDR-GNB, especially CRE and CRAB [12], were assessed.

2. Materials and methods

2.1. Study design and objectives

This observational, cross-sectional study was conducted in 22 Italian centres [20 hospitals plus 2 intensive care units (ICUs)]. The complete list of participating centres is available in Supplementary Table S1, whilst their geographical distribution is shown in Fig. 1. The study was first approved by the Ethics Committee of the coordinating centre (Ospedale Policlinico San Martino–IRCCS, Genoa, Italy) and subsequently by the Ethics Committees of the other 21 participating centres. After receiving approval from the pertinent local ethics committee, all adult patients starting colistin treatment during a consecutive 3-month period were prospectively included in the study. The 3-month enrolment period started in March 2018 in the first activated centre and finished in September 2018 in the last activated centre. Data were collected at the time of colistin initiation with no follow-up, in line with the cross-sectional design and the objectives of the study. All conscious patients signed an informed consent to participate in the study. A waiver of informed consent for patients unconscious at the time of colistin initiation was obtained in most participating centres (only five unconscious patients were not enrolled).

Patients were included in the study only once, at the time of initiation of the first colistin treatment during the study period. The primary objective of the study was to describe the use of colistin in terms of dosages, indications and characteristics of treated patients. The secondary objective was to assess factors associated with the use of colistin in combination with other anti-MDR-GNB agents. Details regarding protocol registration and deviations, sample size calculation and statistical analysis are available in the Supplementary methods.

3. Results

During the study period, 229 adult patients received colistin treatment, of whom 221 (97%) were included in the study (Supplementary Fig. S1). Their median age was 64 years (interquartile range 52–73 years) and 134 (61%) were male.

Fig. 1. Geographical distribution of participating centres. A detailed list of the 22 participating centres is available as Supplementary Table S1.

Table 1 reports the complete demographic and clinical characteristics of the enrolled patients. Of the 221 patients, 32 (14%) had received a previous course of colistin therapy, mostly in combination with other anti-MDR-GNB agents (29/30; 97%). Previous colonisation/infection with at least one carbapenem-resistant organism [CRE, carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) or CRAB] was registered in 62% of patients (138/221), with a 12% (15/121) prevalence of colistin resistance in previous isolates.

Colistin was mostly administered intravenously (203/221; 92%) and mainly for targeted therapy (168/221; 76%). Among 203 cases of intravenous (i.v.) administration, colistin was concomitantly administered as inhaled (20/203; 10%) or intrathecal (3/203; 1%) therapy (Supplementary Table S2). The most frequent indications for colistin administration were sepsis and lower respiratory tract infection (LRTI) for empirical therapy and bloodstream infection (BSI) and LTRI for targeted therapy (Supplementary Table S2). Among 53 cases of empirical therapy, 48 (91%) had a history of previous colonisation/infection by a carbapenem-resistant organism in the patient and/or in other patients hospitalised in the same ward. After starting empirical colistin, an aetiological diagnosis was achieved in 30/53 patients (57%) and CRE, CRAB and CRPA were isolated in 33% (10/30), 30% (9/30), and 7% (2/30) of cases, respectively. CRAB was the most frequent causative agent of infections treated with targeted colistin, being involved as monomicrobial or polymicrobial infections in as many as 85/168 cases (51%). The complete list of aetiological agents is available as Supplementary Table S3.

Colistin susceptibility testing was performed on 183/198 (92%) causative isolates obtained either before or after colistin initiation, mostly using automated systems (145/183; 79%). Broth microdilution as first susceptibility test method or as confirmatory test was performed in 124/183 cases (68%). Gradients tests were employed in 4/183 cases (2%), and in all of them with subsequent broth microdilution confirmation. Colistin susceptibility in causative agents isolated after initiation of empirical colistin was assessed in 15 cases, of which 4 (27%) were colistin-resistant.

Intravenous colistin was administered in combination with at least one other anti-MDR-GNB agent in 80% of cases (163/203). A loading dose of 9 million units (MU) of colistimethate was administered in 79% of patients receiving i.v. colistin, whereas adherence to the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) recommendations [13] for prescribed maintenance dosages was 85% (Table 2).

Table 1
Demographic and clinical characteristics of adult patients treated with colistin.

Variable	No. of patients[a]	%	95% CI
Demographic characteristics			
Age (years) [median (IQR)]	64 (52–73)		62–67
Male sex	134/221	61	54–67
Medical history			
Previous hospitalisation (within 6 months)	124/221	56	49–63
Diabetes mellitus	55/221	25	19–31
Chronic renal failure	45/221	20	15–26
Solid neoplasm	40/221	18	13–24
Haematological malignancy	16/221	7	4–11
Charlson comorbidity index [median (IQR)]	2 (1–3)		2–2
Previous treatment with colistin[b]	32/221	15	10–20
Anti-MDR-GNB monotherapy	1/30	3	0–16
Anti-MDR-GNB combination therapy	29/30	97	84–100
Unknown whether monotherapy or combination	2/32		
Hospital stay before colistin initiation (days) [median (IQR)]	21 (10–43)		17–25
Microbiological history			
Previous colonisation/infection by CRE			
In the patient	89/221	40	34–47
Colistin-resistant	8/77	10	5–19
(Colistin not tested)	(12)		
In other patients in the same ward [c]	142/221	64	58–70
Colistin-resistant	26/135	19	13–27
(Colistin not tested)	(7)		
Previous colonisation/infection by CRPA			
In the patient	17/221	8	5–12
Colistin-resistant	0/16	0	0–2
(Colistin not tested)	(1)		
In other patients in the same ward[c]	32/221	15	10–20
Colistin-resistant	3/31	10	3–25
(Colistin not tested)	(1)		
Previous colonisation/infection by CRAB			
In the patient	55/221	25	19–31
Colistin-resistant	7/50	14	6–27
(Colistin not tested)	(5)		
In other patients in the same ward[c]	94/221	43	36–49
Colistin-resistant	15/94	16	10–25
(Colistin not tested)	(0)		
Previous colonisation/infection by CRE, CRPA and/or CRAB			
In the patient	138/221	62	56–69
Colistin-resistant	15/121	12	7–20
(Colistin not tested)	(17)		
In other patients in the same ward[c]	165/221	75	68–80
Colistin-resistant	39/158	25	18–32
(Colistin not tested)	(7)		
Baseline variables[c]			
Ward			
ICU	96/221	43	37–50
Medical ward	80/221	36	30–43
Surgical ward	33/221	15	11–20
Rehabilitation ward	12/221	5	3–9
Presence of CVC	165/221	75	68–80
Presence of urinary catheter	179/221	81	75–86
Mechanical ventilation	66/221	30	24–36
Septic shock	43/221	19	15–25
Neutropenia	14/221	6	4–10
Serum albumin (g/dL) [median (IQR)][d]	2.6 (2.3–3.0)		2.6–2.8
Missing (serum albumin not tested)	22/221		
Serum creatinine (mg/dL) [median (IQR)][d]	0.8 (0.6–1.3)		0.7–0.9
Haemodialysis	15/221	7	4–11
KDIGO stage of AKI			
No AKI	170/221	77	71–82
Stage 1	24/221	11	7–16
Stage 2	12/221	5	3–9
Stage 3	15/221	7	4–11

AKI, acute kidney injury; CI, confidence interval; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRE, carbapenem-resistant Enterobacterales; CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; CVC, central venous catheter; ICU, intensive care unit; IQR, interquartile range; KDIGO, Kidney Disease: Improving Global Outcomes; MDR-GNB, multidrug-resistant Gram-negative bacteria.

[a] Results are presented as no. of patients/total of patients unless otherwise stated.

[b] Previous anti-MDR-GNB combination was defined as previous treatment with colistin in combination with at least one of the following agents: carbapenems; aminoglycosides; fosfomycin; tigecycline; trimethoprim/sulfamethoxazole; rifampicin; ceftazidime/avibactam; and ceftolozane/tazobactam.

[c] At the time of colistin initiation.

[d] Last measured value before colistin initiation.

Table 2
Characteristics of intravenous colistin therapies.

Variable	No. of patients[a]	%	95% CI
Type of therapy			
Empirical therapy	49/203	24	19–30
Targeted therapy[b]	154/203	76	70–81
Type of anti-MDR-GNB therapy			
Colistin monotherapy	40/203	20	15–26
Combination therapy[c]	163/203	80	74–85
Targeted therapy for CRE[d]			
Colistin monotherapy	4/40	10	3–23
Combination therapy[e]	36/40	90	77–97
Targeted therapy for CRPA[d]			
Colistin monotherapy	7/22	32	15–55
Combination therapy[e]	15/22	68	45–85
Targeted therapy for CRAB[d]			
Colistin monotherapy	21/65	32	22–45
Combination therapy [e]	44/65	68	55–78
Dosage			
Administration of loading dose	178/203	88	82–92
Administration of loading dose of 9 MU of CMS[f]	160/203	79	73–84
Adequate daily maintenance dosage of CMS according to estimated CL_{Cr}[g,h] [20]			
All patients	159/187	85	79–90
CL_{Cr} 10 to <30 mL/min (4.50–5.50 MU)	13/18	72	47–88
CL_{Cr} 30 to <50 mL/min (5.50–7.50 MU)	14/22	64	42–81
$CL_{Cr} \geq 50$ mL/min (9.00 MU)	132/147	90	84–94

CI, confidence interval; CL_{Cr}, creatinine clearance; CMS, colistimethate; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRE, carbapenem-resistant Enterobacterales; CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; EMA CHMP, European Medicines Agency Committee for Medicinal Products for Human Use; IQR, interquartile range; MDR-GNB, multidrug-resistant Gram-negative bacteria; MU, million units.

[a] Results are presented as no. of patients/total of patients unless otherwise stated. The denominator ($n = 203$) includes intravenous ($n = 180$), intravenous plus inhaled ($n = 20$) and intravenous plus intrathecal ($n = 3$) colistin therapies.

[b] Post-identification of the causative agent.

[c] Anti-MDR-GNB combination was defined as treatment with colistin in combination with at least one of the following agents: carbapenems; aminoglycosides; fosfomycin; tigecycline; trimethoprim/sulfamethoxazole; rifampicin; ceftazidime/avibactam; ceftolozane/tazobactam; and any other anti-Gram-negative agent administered in combination with colistin for the intended treatment of a suspected or proven MDR-GNB infection.

[d] Analyses limited to monomicrobial infections due to CRE, CRPA or CRAB.

[e] Colistin companion agents for CRE infections: meropenem ($n = 11$); fosfomycin + meropenem ($n = 5$); fosfomycin + tigecycline ($n = 4$); meropenem + tigecycline ($n = 3$); tigecycline ($n = 3$); fosfomycin ($n = 2$); gentamicin + meropenem ($n = 2$); amikacin + ceftazidime/avibactam + tigecycline ($n = 1$); ceftazidime/avibactam ($n = 1$); ceftazidime + levofloxacin ($n = 1$); ceftazidime/avibactam + meropenem ($n = 1$); ertapenem + meropenem ($n = 1$); and gentamicin + tigecycline ($n = 1$). Colistin companion agents for CRPA infections: meropenem ($n = 6$); ceftolozane/tazobactam ($n = 3$); amikacin ($n = 1$); amikacin + meropenem ($n = 1$); ceftazidime/avibactam ($n = 1$); ceftolozane/tazobactam + meropenem ($n = 1$); imipenem ($n = 1$); piperacillin/tazobactam ($n = 1$). Colistin companion agents for CRAB infections: meropenem ($n = 15$); meropenem + tigecycline ($n = 5$); rifampicin ($n = 5$); tigecycline ($n = 4$); ampicillin/sulbactam + meropenem ($n = 2$); rifampicin + tigecycline ($n = 2$); amikacin ($n = 1$); ampicillin/sulbactam ($n = 1$); ampicillin/sulbactam + rifampicin ($n = 1$); cefepime ($n = 1$); ceftolozane/tazobactam + tigecycline ($n = 1$); trimethoprim/sulfamethoxazole + tigecycline ($n = 1$); fosfomycin + meropenem + rifampicin + tigecycline ($n = 1$); gentamicin + meropenem ($n = 1$); imipenem ($n = 1$); and meropenem + rifampicin ($n = 2$).

[f] As recommended by the EMA CHMP both in patients with and without impaired renal function, including those receiving renal replacement therapy [13].

[g] In patients not receiving haemodialysis (188/203). Maintenance dose information missing for 1 patient (final denominator = 187). The last two serum creatinine values before colistin initiation were collected to estimate CL_{Cr} according to the Jelliffe formula.

[h] Overall, 184/203 patients treated with intravenous colistin therapy (91%) received maintenance dosages in two daily doses.

In the univariable analysis, mechanical ventilation, presence of septic shock, empirical therapy, targeted therapy for CRE infections and i.v. administration showed a statistically significant association with the use of colistin in combination, whereas chronic renal failure and targeted therapy of CRAB infections were associated with use of colistin monotherapy (Supplementary Table S4). In the multivariable analysis (model A), only empirical therapy [odds ratio (OR) = 3.25, 95% confidence interval (CI) 1.24–8.53; $P = 0.017$], targeted therapy for CRE infections (OR = 4.76, 95% CI 1.69–13.43; $P = 0.003$) and chronic renal failure (OR = 0.39, 95% CI 0.17–0.88; $P = 0.024$) retained statistically significant associations (Supplementary Table S5). Supplementary Table S5 also shows the results of the additional multivariable model with centre as a random effect (model B), which largely confirmed the associations observed in model A (although with borderline significance for chronic renal failure, possibly because of reduced power), but also indicated i.v. administration as a further variable associated with combination therapy.

4. Discussion

In a cohort of 221 patients from 22 Italian centres, colistin was mostly used intravenously and in combination with other anti-MDR-GNB agents, mainly for the targeted therapy of LRTIs and BSIs caused by carbapenem-resistant organisms.

Use of colistin in the USA and Europe has recently been explored by Wenzler et al. with an electronic questionnaire survey distributed to 420 physicians asking about their routine use of colistin [14]. The respondents indicated that they administer polymyxins mainly for pneumonia (63%) and for suspected/proven carbapenem-resistant infections (85%) [14], which is in line with the current findings. In addition, the current study also directly measured the actual proportion of empirical use of colistin, which was 24% versus 76% for targeted therapy. Of note, this preference towards restricting the use of colistin for targeted therapy, possibly relying on the intention of avoiding nephrotoxic agents in empirical therapy, could theoretically help to delay the emergence of colistin resistance. It is also worth noting that on no occasion was colistin used for selective digestive decontamination, possibly reflecting the intention to avoid further selective pressure for resistance in a country already endemic for CRE [15–17].

In the present study, the level of adequateness of i.v. colistin dosages was measured according to the EMA CHMP review of polymyxin-based medicines [13], observing a high proportion both of adequate loading doses (79%) and adequate maintenance dosages (85%). These results are in line with the fact that

antimicrobial stewardship interventions to increase the optimal use of this last-resort agent have been already implemented in Italian hospitals [18], but they also clearly identify specific points where further improvements are still needed, mainly tailored interventions for reducing the missing 21% of adequate loading dosage. In addition, it should be noted that international consensus guidelines regarding the optimal use of polymyxins have been published very recently (after performance of the present study) that indicate the possible need for increased maintenance dosages in patients with creatinine clearance >80 mL/min, in line with the most recent pharmacokinetic/pharmacodynamic evidence [19]. If validated in confirmatory studies, this will likely become common practice in the future in order not to risk suboptimal exposures in patients without renal function impairments [19].

Most patients in this study received colistin as part of a combination for the treatment of a suspected or proven infection due to MDR-GNB. In this regard, the possible survival benefit of using combinations for treating severe CRE infections, previously reported in observational studies [10], might contribute to explaining the independent association found between use of colistin in combination and both targeted therapy of CRE and empirical therapy (need for CRE coverage). None the less, although less frequently than for CRE infections, it is worth noting that colistin was also mainly used in combinations for treating CRPA and CRAB (e.g. as i.v. treatment, combined regimens were preferred to monotherapy in 90% of monomicrobial CRE infections but also in 68% of monomicrobial CRPA infections and 68% of monomicrobial CRAB infections). On the one hand, the non-negligible proportion of patients with CRPA and CRAB treated with combinations may be in line with the intention of clinicians to deal with the possible suboptimal pharmacokinetics of colistin by adding another agent, hoping for synergy or just for additive effects. On the other hand, the reduced use of combinations for CRPA and CRAB in comparison with CRE possibly reflects the lack of evidence for CRPA (only a few small observational studies exploring the use of colistin-based combinations for CRPA have been conducted) and the results of the AIDA randomised controlled trial for CRAB [2]. In this latter study, Paul et al. found that addition of meropenem to colistin did not reduce the rate of clinical failure in patients with severe CRAB infections, thus casting doubts about the use of colistin plus meropenem combinations for CRAB [2]. However, it is of note that carbapenems were employed in as much as 61% of colistin-based combinations used for CRAB infections in the current study, possibly reflecting the lack of other therapeutic options [20].

With regard to other factors associated with use of colistin in combination or as monotherapy in this study, the association found between chronic renal failure and monotherapy may partly depend on the unwillingness to combine colistin with other nephrotoxic agents (i.e. aminoglycosides), even when they remain the only other dependable option. The association between i.v. administration and use in combination found in the additional mixed multivariable model may reflect the preferential use of combinations for treating severe infections, which usually require i.v. therapy.

The present study has some limitations. The first is that follow-up data were not collected, thus rates of clinical response to colistin treatment and survival could not be assessed. However, the main aim was to focus on the characteristics of colistin prescription patterns and the study was thus designed to optimise the collection of cross-sectional descriptive data (e.g. for adequately describing the heterogeneity in colistin treatment) rather than for assessing the impact on outcome of colistin therapy (where heterogeneity usually implies considerable confounding effects). Another limitation is that we were unable to register detailed data on the type of haemodialysis (e.g. intermittent haemodialysis, sustained low-efficiency dialysis, continuous renal replacement therapy). Consequently, the adequateness of maintenance dosages in the 15 patients who received haemodialytic treatment could not be evaluated. It should also be noted that despite the large sample size, peculiar characteristics of some participating centres (e.g. two participated only as ICUs, one centre is specialised in solid-organ transplants, and another one is specialised in neurorehabilitation) might partly limit the generalisability of the results. Finally, no phenotypic or molecular information regarding carbapenem and colistin resistance determinants was collected.

In conclusion, colistin remains an important option for severe MDR-GNB infections when other options are not available. Colistin was mostly used appropriately according to recommendations available at the time of the study in a country endemic for MDR-GNB organisms, although the results also indicate that targeted efforts might be necessary for further increasing the rate of adequate loading dosages. The recent availability and dissemination of international consensus guidelines based on updated information might further improve the use of this last-resort drug in the future.

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Competing interests

CV and DRG are among the authors of the International Consensus Guidelines for the optimal use of polymyxins. All other authors declare no competing interests.

Ethical approval

Liguria Region Ethics Committee [registry no. 321REG2017].

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jgar.2019.06.009.

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