Title: Use of colistin in adult patients: a cross-sectional study

Authors: Daniele Roberto Giacobbe, Carolina Saffioti, Angela Raffaella Losito, Matteo Rinaldi, Caterina Aurilio, Cesare Bolla, Silvia Boni, Guglielmo Borgia, Novella Carannante, Giovanni Cassola, Giancarlo Ceccarelli, Silvia Corcione, Daniela Dalla Gasperina, Francesco Giuseppe De Rosa, Chiara Dentone, Stefano Di Bella, Nicoletta Di Lauria, Marcello Feasi, Marco Fiore, Sara Fossati, Erica Franceschini, Andrea Gori, Guido Granata, Sara Grignolo, Paolo Antonio Grossi, Giuliana Guadagnino, Filippo Lagi, Alberto Enrico Maraolo, Valeria Marinò, Maria Mazzitelli, Alessandra Mularoni, Alessandra Oliva, Maria Caterina Pace, Andrea Parisini, Francesca Patti, Nicola Petrosillo, Vincenzo Pota, Francesca Raffaelli, Marianna Rossi, Antonella Santoro, Carlo Tascini, Carlo Torti, Enrico Maria Trecarichi, Mario Venditti, Pierluigi Viale, Alessio Signori, Matteo Bassetti, Valerio Del Bono, Maddalena Giannella, Malgorzata Mikulska, Mario Tumbarello, Claudio Viscoli, on behalf of SITA GIOVANI, (young investigators group of the Società Italiana Terapia Antinfettiva), the COLI-CROSS study group

PII: S2213-7165(19)30153-5
DOI: https://doi.org/10.1016/j.jgar.2019.06.009
Reference: JGAR 965

To appear in:

Received date: 1 April 2019
Revised date: 3 June 2019
Accepted date: 8 June 2019

Please cite this article as: Giacobbe DR, Saffioti C, Losito AR, Rinaldi M, Aurilio C, Bolla C, Boni S, Borgia G, Carannante N, Cassola G, Ceccarelli G, Corcione S, Gasperina DD, De Rosa FG, Dentone C, Di Bella S, Di Lauria N, Feasi M, Fiore M, Fossati S, Franceschini E, Gori A, Granata G, Grignolo S, Grossi PA, Guadagnino G, Lagi F, Maraolo AE, Marinò V, Mazzitelli M, Mularoni A, Oliva A, Pace MC, Parisini A, Patti F, Petrosillo N, Pota V, Raffaelli F, Rossi M, Santoro A, Tascini C, Torti C, Trecarichi EM, Venditti M, Viale P, Signori A, Bassetti M, Del Bono V, Giannella M, Mikulska M, Tumbarello M, Viscoli C, Use of colistin in adult

patients: a cross-sectional study, *Journal of Global Antimicrobial Resistance* (2019), https://doi.org/10.1016/j.jgar.2019.06.009

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

Daniele Roberto Giacobbe[1]*, Carolina Saffioti[1,2], Angela Raffaella Losito[3], Matteo Rinaldi[4], Caterina Aurilio[5], Cesare Bolla[6], Silvia Boni[7], Guglielmo Borgia[8], Novella Carannante[9], Giovanni Cassola[10], Giancarlo Ceccarelli[11], Silvia Corcione[12], Daniela Dalla Gasperina[13], Francesco Giuseppe De Rosa[12], Chiara Dentone[14], Stefano Di Bella[15], Nicoletta Di Lauria[16], Marcello Feasi[10], Marco Fiore[17], Sara Fossati[15], Erica Franceschini[18], Andrea Gori[19], Guido Granata[20], Sara Grignolo[7], Paolo Antonio Grossi[13], Giuliana Guadagnino[21], Filippo Lagi[16], Alberto Enrico Maraolo[8], Valeria Marinò[22], Maria Mazzitelli[23], Alessandra Mularoni[21], Alessandra Oliva[11,22], Maria Caterina Pace[17], Andrea Parisini[6], Francesca Patti[14], Nicola Petrosillo[20], Vincenzo Pota[5], Francesca Raffaelli[3], Marianna Rossi[24], Antonella Santoro[18], Carlo Tascini[9], Carlo Torti[23], Enrico Maria Trecarichi[23], Mario Venditti[11], Pierluigi Viale[4], Alessio Signori[1], Matteo Bassetti[25], Valerio Del Bono[26], Maddalena Giannella[4], Malgorzata Mikulska[1,2], Mario Tumbarello[3], Claudio Viscoli[1,2]; on behalf of SITA GIOVANI (young investigators group of the Società Italiana Terapia Antinfettiva) and the COLI-CROSS study group

[1] Department of Health Sciences, University of Genoa, Genoa, Italy

[2] Ospedale Policlinico San Martino - IRCCS, Genoa, Italy

[3] Fondazione Policlinico Universitario A. Gemelli IRCCS – Università Cattolica del Sacro Cuore, Rome, Italy

[4] Department of Medical and Surgical Sciences, Infectious Diseases Unit, Alma Mater Studiorum University of Bologna, Italy

[5] Anaesthesia and Intensive Care Unit, Department of Women, Children, General and Specialistic Surgery, L. Vanvitelli University of Campania, Naples, Italy

[6] SC Malattie Infettive, ASO SS. Antonio e Biagio e Cesare Arrigo, Alessandria, Italy

[7] Divisione di Malattie Infettive, Ospedale Sant'Andrea, La Spezia, Italy

[8] Section of Infectious Diseases, Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy

[9] First Division of Infectious Diseases, Cotugno Hospital, AORN dei Colli, Naples, Italy

[10] Department of Infectious Diseases, Galliera Hospital, Genoa, Italy

[11] Department of Public Health and Infectious Diseases, Sapienza University of Rome, Policlinico Umberto I, Rome, Italy

[12] Department of Medical Sciences, Infectious Diseases, University of Turin, Turin, Italy

[13] Infectious and Tropical Diseases Unit, Department of Medicine and Surgery, University of Insubria, Varese, Italy

[14] Medical Department, Infectious Diseases Unit, Sanremo Hospital, Imperia, Italy

[15] Infectious Diseases Department, Azienda Sanitaria Universitaria Integrata di Trieste, Trieste, Italy

[16] Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy

[17] Department of Anaesthesiological, Surgical and Emergency Sciences, University of Campania "Luigi Vanvitelli", Naples, Italy

[18] Clinic of Infectious Diseases, University of Modena and Reggio Emilia, Modena, Italy

[19] University of Milan and Infectious Diseases Unit, Department of Internal Medicine, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

[20] Clinical and Research Department for Infectious Diseases, Severe and Immunedepression-Associated Infections Unit, National Institute for Infectious Diseases L. Spallanzani, IRCCS, Rome, Italy

[21] Infectious Diseases ISMETT IRCCS, Palermo, Italy

[22] IRCCS INM Neuromed, Pozzilli, Italy

[23] Department of Medical and Surgical Sciences, Infectious and Tropical Diseases Unit, "Magna Graecia" University of Catanzaro, Catanzaro, Italy

[24] Clinic of Infectious Diseases, San Gerardo Hospital, University of Milano-Bicocca, Monza, Italy

[25] Department of Medicine, University of Udine and Azienda Sanitaria Universitaria Integrata, Udine, Italy

[26] Infectious Diseases Unit, Azienda Ospedaliera S. Croce e Carle, Cuneo, Italy

*** Corresponding author:**

Daniele Roberto Giacobbe

University of Genoa, Dipartimento di Scienze della Salute (DISSAL)

Via Antonio Pastore, 1 – 16132 Genoa, Italy

Telephone: +39 010 555 4652; Fax: +39 010 5556712

Email address: daniele.roberto.giacobbe@gmail.com

COLI-CROSS study group (collaborators): F. Alessandri, A. Alfieri, R.M. Antonello, S. Argentero, S. Artioli, M. Bartoletti, A. Bartoloni, S. Beltramini, I. Bisso, S. Buono, A.R. Buonomo, D. Bianchi, E. Blasi Vacca, M. Canepa, A. Capone, G. Chichino, G. De Benedectis, G. Di Caprio, Z. Di Rosa, F. Di Zazzo, I. Gentile, G. Greco, T. Lupia, R. Luzzati, A. Milano, S. Mornese Pinna, C. Mussini, M.B. Passavanti, C. Rogati, A.

Russo, P. Sansone, G. Sarteschi, F. Serapide, M. Spaziante, F. Taglietti, S. Tedeschi, R.F. Tobaldi.

Highlights

- In a country endemic for multidrug-resistant Gram-negative bacteria (MDR-GNB), colistin was mostly administered in combination with at least another anti-MDR-GNB agent
- A loading dose of 9 million units of colistimethate was administered in 79% of patients, and adequate maintenance doses in 85%
- Empirical therapy and targeted therapy of carbapenem-resistant Enterobacterales infections were associated with use of colistin in combinations with other agents, while chronic renal failure was associated with use of colistin as monotherapy
- Although colistin was mostly used appropriately, our results also indicate that targeted efforts might be necessary for further increasing rates of adequate loading dosages.

Abstract

Objectives: The objective of this study was to assess the use of colistin in a country endemic for multidrug-resistant Gram-negative bacteria (MDR-GNB).

Methods: Colistin prescription patterns were evaluated in 22 Italian centers. Factors associated with use of colistin in combination with other anti-MDR-GNB agents were also assessed.

Results: During the study period, 221 adults receiving colistin were included in the study. Their median age was 64 years (interquartile range 52-73), and 134 were males (61%). 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 million units of colistimethate was administered in 79% of patients, and adequate maintenance doses in 85%. In multivariable analysis, empirical therapy (odds ratio [OR] 3.25, 95% confidence intervals [CI] 1.24-8.53, p = 0.017) and targeted therapy of carbapenem-resistant *Enterobacterales* infections (OR 4.76, 95% CI 1.69-13.43, p = 0.003) were associated with use of colistin in combinations with other agents, while chronic renal failure (OR 0.39, 95% CI 0.17-0.88, p = 0.024) was associated with use of colistin as monotherapy.

Conclusions: Colistin remains an important option for severe MDR-GNB infections when other treatments are not available. Despite inherent difficulties in optimizing its use due to peculiar PK/PD characteristics, colistin was mostly used appropriately in a country endemic for MDR-GNB.

Keywords: colistin; colistimethate; *Acinetobacter*; *Pseudomonas*; *Klebsiella*; antimicrobial resistance.

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 a reduction in its use will likely be observed in the near future due to the recent marketing of some 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, the use of colistin should be reserved for these indications and avoided in presence of dependable alternatives, since its effectiveness and safety can be impaired by several factors: (*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 research laboratories; (*iv*) unintended treatment of colistin-resistant infections due to possible limitations of some classical susceptibility testing methods [9]. Therefore, using colistin appropriately (e.g., correct indications, correct dosages, reserving it for infections caused by, or strongly suspected to be caused by, MDR-GNB) is certainly difficult, but also of paramount importance for improving patients' outcome 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 optimize colistin use

and to preserve its activity in the long term. In this cross-sectional study, we assessed prescription patterns of colistin in adult patients in Italy, which is a country endemic for MDR-GNB, especially CRE and CRAB [12].

2. Material and methods

2.1. Study design and objectives

The present observational, cross-sectional study was conducted in 22 Italian centers (20 hospitals plus 2 intensive care units). The complete list of participating centers is available as supplementary material (supplementary table S1), while their geographical distribution is shown in figure 1. The study was first approved by the ethics committee of the coordinating center (Ospedale Policlinico San Martino – IRCCS, Genoa; ethics committee registry number 321REG2017) and subsequently by the ethics committees of the other 21 participating centers. After receiving approval from the pertinent local ethic committee, all adult patients starting colistin treatment during a consecutive 3-month period were prospectively included in the study. The 3-month enrollment period started in March 2018 in the first activated center and finished in September 2018 in the last activated center. Data was 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 centers (only 5 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 as supplementary methods.

3. Results

During the study period, 229 adult patients received colistin treatment, and 221 of them (97%) were included in the study (supplementary figure S1). Their median age was 64 years (interquartile range [IQR] 52-73), and 134 were males (61%).

Table 1 reports the complete demographic and clinical characteristics of enrolled patients. Thirty-two of 221 patients (15%) had received a previous course of colistin therapy, mostly in combination with other anti-MDR-GNB agents (97%). Previous colonization/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 12% prevalence of colistin resistance in previous isolates.

Colistin was mostly administered intravenously (203/221, 92%), and mainly for targeted therapy (168/221, 76%). In 20/203 (10%) and 3/203 (1%) cases of intravenous administration, colistin was concomitantly administered as inhaled or intrathecal therapy, respectively (supplementary table S2). The most frequent indications for colistin administration were sepsis and lower respiratory tract infection for empirical therapy, and bloodstream infection and lower respiratory tract infection for targeted therapy (supplementary table S2). In 48/53 cases of empirical therapy (91%) there was a history of previous colonization/infection by carbapenem-resistant organisms in the patient and/or in other patients hospitalized in the same ward. After starting empirical colistin, etiological 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 much as 85/168 cases (51%). The complete list of etiological agents is available as supplementary material (supplementary table S3).

Colistin susceptibility test was performed on 183/198 causative isolates (92%), obtained either before or after colistin initiation, mostly with 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, and 4/15 were colistin-resistant (27%).

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 of colistimethate was administered in 79% of patients receiving intravenous 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).

In univariable analysis, mechanical ventilation, presence of septic shock, empirical therapy, targeted therapy of CRE infections, and intravenous administration showed a statistically significant association with use of colistin in combination, whereas chronic renal failure and targeted therapy of CRAB infections were associated with use of colistin as monotherapy (supplementary table S4). In multivariable analysis (model A), only empirical therapy (odds ratio [OR] 3.25, 95% confidence intervals [CI] 1.24-8.53, p = 0.017), targeted therapy of 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). Table S5 also shows the results of the additional multivariable model with center 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 intravenous administration as a further variable associated with combination therapy.

4. Discussion

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

The use of colistin in US and Europe has been recently explored by Wenzler and colleagues with an electronic questionnaire survey distributed to 420 physicians asking about their routine use of colistin [14]. Their respondents indicated that they administer polymyxins mainly for pneumonia (63%), and for suspected/proven carbapenem-resistant infections (85%), which is in line with our findings [14]. Additionally, our study also directly measured the actual proportion of empirical use of colistin, which was 24% vs. 76% 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 in no occasion colistin was 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, we measured the level of adequateness of intravenous colistin dosages according to the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) review of polymyxin-based medicines [13], observing a high proportion of both 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 conduction of the present study), that indicate the possible need for increased maintenance dosages in patients with creatinine clearance (CrCl) > 80 ml/min, in line with the most recent PK/PD 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 our study received colistin as part of combinations for the treatment of a suspected or proven infection due to MDR-GNB. In this regard, the possible survival benefit by using combinations for treating severe CRE infections, previously reported in observational studies [10], might contribute explaining the independent association we found between use of colistin in combination and both targeted therapy of CRE and empirical therapy (need for CRE coverage). Nonetheless, 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 intravenous 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 PK 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 randomized controlled trial for CRAB [2]. In this latter study,

Paul and colleagues found that the addition of meropenem to colistin did not reduce the rates 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 our study, possibly reflecting the lack of other therapeutic options [20].

With regard to the other factors associated with use of colistin in combination or as monotherapy in our study, the association we 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 intravenous administration and the use in combination, found in the additional mixed multivariable model, may reflects the preferential use of combinations for treating severe infections, which usually require intravenous therapy.

The present study has some limitations. The first is that we did not collect follow-up data, thus rates of clinical response to colistin treatment and survival could not be assessed. However, our major aim was to focus on the characteristics of colistin prescription patterns, and the study was thus designed in order to optimize 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 hemodialysis (e.g., intermittent hemodialysis, sustained low efficiency dialysis, continuous renal replacement therapy). Consequently, the adequateness of maintenance dosages in the fifteen patients who received hemodialytic treatment

could not be evaluated. It should also be noted that, despite the large sample size, peculiar characteristics of some participating centers (e.g., two participated only as ICUs, one center is specialized in solid organ transplants, and another one is specialized neurorehabilitation) might partly limit the generalizability of our results. Finally, no phenotypical 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 our results also indicate that targeted efforts might be necessary for further increasing rates 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.

Declarations

Funding: This work is partially supported by a grant from the Società Italiana di Terapia Antinfettiva ("Borsa di Studio S.I.T.A. per ricerche su infezioni batteriche e fungine").

Competing Interests: CV and DRG are among the authors of the International Consensus Guidelines for the optimal use of the polymyxins. The other authors report no conflicts of interest relevant to this study.

Ethical Approval: Liguria Region Ethics committee registry number 321REG2017

References

1. Bassetti M, Giacobbe DR, Giamarellou H, et al. Management of KPC-producing Klebsiella pneumoniae infections. Clin Microbiol Infect 2018; 24(2): 133-44.

2. Paul M, Daikos GL, Durante-Mangoni E, et al. Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial. Lancet Infect Dis 2018; 18(4): 391-400.
3. Zusman O, Altunin S, Koppel F, Dishon Benattar Y, Gedik H, Paul M. Polymyxin monotherapy or in combination against carbapenem-resistant bacteria: systematic review and meta-analysis. J Antimicrob Chemother 2017; 72(1): 29-39.
4. Giacobbe DR, Bassetti M, De Rosa FG, et al. Ceftolozane/tazobactam: place in therapy. Expert Rev Anti Infect Ther 2018: 1-14.
5. Pogue JM, Bonomo RA, Kaye KS. Ceftazidime/avibactam, Meropenem/vaborbactam or both? Clinical and formulary considerations. Clin Infect Dis 2018.
6. van Duin D, Lok JJ, Earley M, et al. Colistin Versus Ceftazidime-Avibactam in the Treatment of Infections Due to Carbapenem-Resistant Enterobacteriaceae. Clin Infect Dis 2018; 66(2): 163-71.
7. Pogue JM, Ortwine JK, Kaye KS. Clinical considerations for optimal use of the polymyxins: A focus on agent selection and dosing. Clin Microbiol Infect 2017; 23(4): 229-33.
8. Cheah SE, Wang J, Nguyen VT, Turnidge JD, Li J, Nation RL. New pharmacokinetic/pharmacodynamic studies of systemically administered colistin against Pseudomonas aeruginosa and Acinetobacter baumannii in mouse thigh and lung infection models: smaller response in lung infection. J Antimicrob Chemother 2015; 70(12): 3291-7.

9. Matuschek E, Ahman J, Webster C, Kahlmeter G. Antimicrobial susceptibility testing of colistin - evaluation of seven commercial MIC products against standard broth microdilution for Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, and Acinetobacter spp. Clin Microbiol Infect 2018; 24(8): 865-70.

10. Tumbarello M, Trecarichi EM, De Rosa FG, et al. Infections caused by KPC-producing Klebsiella pneumoniae: differences in therapy and mortality in a multicentre study. J Antimicrob Chemother 2015; 70(7): 2133-43.

11. Zak-Doron Y, Dishon Benattar Y, Pfeffer I, et al. The Association between Empirical Antibiotic Treatment and Mortality in Severe Infections Caused by Carbapenem-Resistant Gram-Negative Bacteria: A Prospective Study. Clin Infect Dis 2018.

12. Antimicrobial resistance surveillance in Europe. Annual report of the European Antimicrobial Resistance Surveillance Network (EARSNet) 2017. Stockholm: ECDC; 2018 [cited 2018 Dec 19]. Available from: https://ecdc.europa.eu/sites/portal/files/documents/AMR-surveillance-EARS-Net-2017-updated-dec-18.pdf.

13. European Medicines Agency completes review of polymyxin-based medicines. Recommendations issued for safe use in patients with serious infections resistant to standard antibiotics. Annex III. https://www.ema.europa.eu/documents/referral/polymyxin-article-31-referral-annex-iii_en.pdf.

14. Wenzler E, Bunnell KL, Danziger LH. Clinical use of the polymyxins: the tale of the fox and the cat. Int J Antimicrob Agents 2018; 51(5): 700-6.

15. Bassetti M, Righi E. SDD and colistin resistance: end of a dream? Intensive Care Med 2014; 40(7): 1066-7.

16. Giani T, Pini B, Arena F, et al. Epidemic diffusion of KPC carbapenemase-producing Klebsiella pneumoniae in Italy: results of the first countrywide survey, 15 May to 30 June 2011. Euro Surveill 2013; 18(22).

17. Giacobbe DR, Del Bono V, Trecarichi EM, et al. Risk factors for bloodstream infections due to colistin-resistant KPC-producing Klebsiella pneumoniae: results from a multicenter case-control-control study. Clin Microbiol Infect 2015; 21(12): 1106.e1-8.

18. Giacobbe DR, Del Bono V, Mikulska M, et al. Impact of a mixed educational and semi-restrictive antimicrobial stewardship project in a large teaching hospital in Northern Italy. Infection 2017; 45(6): 849-56.

19. Tsuji BT, Pogue JM, Zavascki AP, et al. International consensus guidelines for the optimal use of the polymyxins: recommendations from ACCP, ESCMID, IDSA, ISAP, and SIDP. Pharmacotherapy 2019. doi: 10.1002/phar.2209.

20. Giacobbe DR, Mikulska M, Viscoli C. Recent advances in the pharmacological management of infections due to multidrug resistant gram-negative bacteria. Expert Rev Clin Pharmacol 2018; 11(12): 1219-1236.

Figure 1. Geographical distribution of participating centers

Figure 1 legend

The detailed list of the 22 participating center is available as supplementary material (table S1)

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

Variable	No. of patients*	%	95% CI
Demographic variables			
Age in years, median (IQR)	64 (52-73)		62-67
Male gender	134/221	61	54-67
Medical history			
Previous hospitalization (6 month)	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
Hematological malignancy	16/221	7	4-11
Charlson score, median (IQR)	2 (1-3)		2-2
Previous treatment with colistin**	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 if monotherapy or combinations	2/32		
Hospital stay before colistin initiation in days, median (IQR)	21 (10-43)		17-25
Microbiological history			
Previous colonization/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§	142/221	64	58-70
Colistin-resistant	26/135	19	13-27
(Colistin not tested)	(7)		
Previous colonization/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[§]	32/221	15	10-20
Colistin-resistant	3/31	10	3-25
(Colistin not tested)	(1)		
Previous colonization/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[§]	94/221	43	36-49
Colistin-resistant	15/94	16	10-25
(Colistin not tested)	(0)		
Previous colonization/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[§]	165/221	75	68-80
Colistin-resistant	39/158	25	18-32
(Colistin not tested)	(7)		
Baseline variables[§]			
Ward of staying			
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 in g/dl[§§], median (IQR)	2.6 (2.3-3.0)		2.6-2.8
Missing (serum albumin not tested)	22/221		

Serum creatinine in mg/dl[§§], median (IQR)	0.8 (0.6-1.3)		0.7-0.9
Hemodialysis	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; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRE, carbapenem-resistant *Enterobacterales*; CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; CI, confidence intervals; CVC, central venous catheter; ICU, intensive care unit; IQR, interquartile range; KDIGO, Kidney Disease: Improving Global Outcomes; MDR-GNB, multidrug-resistant Gram-negative bacteria.

*Results are presented as No. of patients/Total of patients unless otherwise indicated.

** 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; cotrimoxazole; rifampin; ceftazidime/avibactam; ceftolozane/tazobactam.

[§] At the time of colistin initiation

[§§] Last measured value before colistin initiation

Table 2. Characteristics of intravenous colistin therapies

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

CI, confidence intervals; CMS, colistimethate; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CrCl, creatinine clearance; 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.

*Results are presented as No. of patients/Total of patients unless otherwise indicated. The denominator (n = 203) includes intravenous (n = 180), intravenous plus inhaled (n = 20), and intravenous plus intrathecal (n = 3) colistin therapies.

** Analyses limited to monomicrobial infections due to CRE, CRPA, or CRAB.

[§] Post-identification of the causative agent

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

[§§§] Colistin companion agents for CRE infections: meropenem (n = 11); fosfomycin plus meropenem (n = 5); fosfomycin plus tigecycline (n = 4); meropenem plus tigecycline (n = 3); tigecycline (n = 3); fosfomycin (n = 2); gentamicin plus meropenem (n = 2); amikacin plus ceftazidime/avibactam plus tigecycline (n = 1); ceftazidime/avibactam (n = 1); ceftazidime plus levofloxacin (n = 1); ceftazidime/avibactam plus meropenem (n = 1); ertapenem plus meropenem (n = 1); gentamicin plus tigecycline (n = 1). Colistin companion agents for CRPA infections: meropenem (n = 6); ceftolozane/tazobactam (n = 3); amikacin (n = 1); amikacin plus meropenem (n = 1); ceftazidime/avibactam (n = 1); ceftolozane/tazobactam plus meropenem (n = 1); imipenem (n = 1); piperacillin/tazobactam (n = 1). Colistin companion agents for CRAB infections: meropenem (n = 15); meropenem plus tigecycline (n = 5); rifampin (n = 5); tigecycline (n = 4); ampicillin/sulbactam plus meropenem (n = 2); rifampin plus tigecycline (n = 2); amikacin (n = 1); ampicillin/sulbactam (n = 1); ampicillin/sulbactam plus rifampin (n = 1); cefepime (n = 1); ceftolozane/tazobactam plus tigecycline (n = 1); cotrimoxazole plus tigecycline (n = 1); fosfomycin plus meropenem plus rifampin plus tigecycline (n = 1);); gentamicin plus meropenem (n = 1); imipenem (n = 1): meropenem plus rifampin (n = 2).

[a] As recommended by the EMA CHMP in both patients with and without impaired renal function, including those in renal replacement therapy [20].

[b] In patients not receiving hemodialysis (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 CrCl according to Jelliffe's formula [19].

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