



Inhaled colistin for the treatment of tracheobronchitis and pneumonia in critically ill children without cystic fibrosis

Matthew E Falagas, Georgia Sideri, Ioanna P. Korbila, Evridiki Vouloumanou, John H. Papadatos, Dimitris A. Kafetzis

► To cite this version:

Matthew E Falagas, Georgia Sideri, Ioanna P. Korbila, Evridiki Vouloumanou, John H. Papadatos, et al.. Inhaled colistin for the treatment of tracheobronchitis and pneumonia in critically ill children without cystic fibrosis. *Pediatric Pulmonology*, 2010, 45 (11), pp.1135. 10.1002/ppul.21302 . hal-00588666

HAL Id: hal-00588666

<https://hal.science/hal-00588666>

Submitted on 26 Apr 2011

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Inhaled colistin for the treatment of tracheobronchitis and pneumonia in critically ill children without cystic fibrosis



Journal:	<i>Pediatric Pulmonology</i>
Manuscript ID:	PPUL-10-0037.R1
Wiley - Manuscript type:	Original Article
Date Submitted by the Author:	19-Mar-2010
Complete List of Authors:	Falagas, Matthew; Alfa Institute of Biomedical Sciences (AIBS), Department of Medicine Sideri, Georgia; Pediatric Intensive Care Unit, P. & A. Kyriakou Children's Hospital, Athens, Greece Korbila, Ioanna; Alfa Institute of Biomedical Sciences (AIBS), Athens, Greece Vouloumanou, Evridiki; Alfa Institute of Biomedical Sciences (AIBS), Athens, Greece Papadatos, John; Pediatric Intensive Care Unit, P. & A. Kyriakou Children's Hospital, Athens, Greece Kafetzis, Dimitris; Second Department of Pediatrics, University of Athens, P. & A. Kyriakou Children's Hospital, Athens, Greece
Keywords:	Gram-negative infections, polymyxins, Pseudomonas, Acinetobacter, intensive care unit



1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

**Inhaled colistin for the treatment of tracheobronchitis and pneumonia
in critically ill children without cystic fibrosis**

Matthew E. Falagas^{1,2,3}, MD, MSc, DSc, Georgia Sideri⁴, MD, Ioanna P. Korbila¹, MD,
Evridiki K. Vouloumanou¹, MD, John H. Papadatos⁴, MD, PhD,
Dimitris A. Kafetzis⁵, MD, PhD

- 1. Alfa Institute of Biomedical Sciences (AIBS), Athens, Greece
- 2. Department of Medicine, Henry Dunant Hospital, Athens, Greece
- 3. Department of Medicine, Tufts University School of Medicine, Boston,
Massachusetts, USA
- 4. Pediatric Intensive Care Unit, P. & A. Kyriakou Children's Hospital, Athens, Greece
- 5. Second Department of Pediatrics, University of Athens, P. & A. Kyriakou Children's
Hospital, Athens, Greece

Corresponding author: Matthew E. Falagas, MD, MSc, DSc
Alfa Institute of Biomedical Sciences (AIBS),
9 Neapoleos Street, 151 23 Marousi, Greece
Tel: +30 (694) 611-0000,
Fax: +30 (210) 683-9605
E-mail: m.falagas@aibs.gr

Short title: Inhaled colistin in children without cystic fibrosis.
Conflict of interest: None
Funding: None
Word counts: abstract: 199, text: 1857
Number of tables: 1
Number of references: 26

Abstract

Data regarding the role of inhaled colistin in critically ill pediatric patients without cystic fibrosis are scarce. Three children (1 female), admitted to the intensive care unit (ICU) of a tertiary-care pediatric hospital in Athens, Greece, during 2004-2009 received inhaled colistin as monotherapy for tracheobronchitis (2 children), and as adjunctive therapy for necrotizing pneumonia (1 child). Colistin susceptible *Acinetobacter baumannii* and *Pseudomonas aeruginosa* were isolated from the cases' bronchial secretions specimens. All 3 children received inhaled colistin in a dosage of 75mg diluted in 3ml of normal saline twice daily (1.875.000 IU of colistin daily), for a duration of 25, 32, and 15 days respectively. The infections improved in all 3 cases. Also, a gradual reduction, and finally total elimination of the microbial load in bronchial secretions was observed during inhaled colistin treatment in the reported cases. All 3 cases were discharged from the ICU. No bronchoconstriction or any other type of toxicity of colistin was observed. In conclusion, inhaled colistin was effective and safe for the treatment of 2 children with tracheobronchitis, and 1 child with necrotizing pneumonia. Further studies are needed to clarify further the role of inhaled colistin in pediatric critically ill patients without cystic fibrosis.

Keywords: Gram-negative infections, polymyxins, *Pseudomonas*, *Acinetobacter*, intensive care unit

Introduction

The use of inhaled antibiotics for the prevention and treatment of difficult-to-treat infections of the respiratory tract has been investigated over the past years. Inhaled tobramycin and colistin are recommended as an early eradication and maintenance therapy in patients with cystic fibrosis and chronic *Pseudomonas aeruginosa* infection.¹⁻³ Inhaled pentamidine is suggested as an alternative prophylactic regimen against *Pneumocystis jirovecii* pneumonia in immunocompromised patients.⁴ Inhaled ribavirin is also used to treat severe infections of the lower respiratory tract in children caused by respiratory syncytial virus (RSV).⁵ Inhaled zanamivir is proven effective for the treatment of influenza infection and the prevention of influenza outbreaks.^{6,7}

The strategy of antimicrobial drug delivery through inhalation has been tested in adult and children population. Specifically, regarding colistin, several studies in adult and pediatric patients with cystic fibrosis have investigated the role of inhaled colistin to eradicate *Pseudomonas aeruginosa*, which chronically colonizes the respiratory tract, as well as its adverse events.⁸⁻¹¹ Patients on mechanical ventilation constitute a high-risk group for difficult-to-treat respiratory infections, including both ventilator-associated tracheobronchitis (VAT) and ventilator-associated pneumonia (VAP).^{12,13} Recent data provide preliminary evidence of inhaled colistin's value to cure difficult-to-treat infections of the respiratory tract caused by multi-drug resistant Gram-negative pathogens such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Klebsiella pneumoniae* in the intensive care unit (ICU) setting in patients without cystic fibrosis.¹⁴⁻¹⁸ On the other hand, in the field of pediatric critical care medicine there is a lack of evidence regarding the role of inhaled colistin to treat such infections.^{19,20}

In this regard, in this small case series we present data regarding critically ill pediatric patients hospitalized in the ICU of a tertiary care pediatric hospital in Athens, Greece, who did not suffer from cystic fibrosis and received inhaled colistin for infections of the lower respiratory tract.

Case description

Children who received inhaled colistin (colistimethate sodium) [1mg equals 12.500 international units (IU) of colistin base activity] in the ICU of the A. & P. Kyriakou tertiary-care pediatric hospital during 2004-2009, were identified by reviewing ICU records. Data presented in this study were extracted from medical charts. Specifically, data regarding the demographical characteristics, underlying disease, reason for ICU admission, length of stay in the ICU and duration of ventilation, type of infection, site of isolation, and susceptibility pattern of each isolated pathogen, whether intravenous colistin was administered prior to inhaled colistin, the device used to deliver inhaled colistin, the type of the ventilator used, and presence of humidification, as well as time of institution, dosage and duration of inhaled colistin treatment, any concomitantly administered antibiotics, quantitative measures of the microbial load, the outcome and any adverse event reported are presented in the Table. The collection and report of the data presented in our study was approved from the hospital's ethical committee. Specifically, this report on inhaled colistin constitutes a nested study within a larger one regarding the toxicity of rarely administered (either intravenously or through inhalation) antimicrobial agents in children.

Case 1

Case 1 was a 10-year-old male suffering from acute disseminated encephalomyelitis attributed to infection with influenza B virus. This child stayed in the ICU for 7 months and developed 5 episodes of septicemia and 2 episodes of septic shock for which he received various antibiotics. Polymyxin-only-susceptible *Acinetobacter baumannii* was isolated in one blood culture, and the infection was cured with the administration of intravenous colistin. The child had a clinical picture of tracheobronchitis, with a high microbial load of *Acinetobacter baumannii* and *Pseudomonas aeruginosa* in cultures of tracheobronchial secretions (the susceptibility pattern of these isolates is presented in the Table). In this regard, inhaled colistin was administered alone at a dosage of 75mg diluted in 3 ml of normal saline twice daily (this equals to a daily dosage of 1.875.000 IU of colistin, administered in 2 divided doses) for 25 days. At day 21 of inhaled colistin treatment, a culture of tracheobronchial secretions with normal flora was obtained. Bronchoconstriction, attributed to the tracheobronchitis, was present before the initiation of inhaled colistin and was unsuccessfully treated with bronchodilators

(specifically, salbutamol, ipratropium). Bronchoconstriction did not worsen during treatment. The outcome of the infection was favorable. However, the child exhibited serious neurological deficiencies that led to the need of permanent tracheostomy and gastrostomy.

Case 2

Case 2 was a 7.5-month-old female with no underlying disease, nor immuno-deficiencies who was admitted at the ICU with septic shock due to necrotizing pneumonia caused by *Pseudomonas aeruginosa*, which was isolated in blood and bronchial secretions cultures obtained at the day of admission in the ICU. The susceptibility pattern of the *Pseudomonas aeruginosa* is presented at the Table. The child received various intravenous antibiotic agents. Inhaled colistin was initiated 3 days after the acquisition of the index cultures at a dosage of 75 mg diluted in 3 ml of normal saline twice daily (a daily dosage of 1.875.000 IU of colistin), administered in 2 divided doses) for 32 days. Concomitant to inhaled colistin administration of intravenous antibiotic regimens included piperacillin/tazobactam and gentamicin for the first 10 days of administration of colistin and meropenem plus vancomycin (due to the isolation of *Staphylococcus* coagulase-negative from blood culture) for the following 11 days. During the course of the infection the child developed bilateral pleural effusions. Culture of the pleural fluid led to *Pseudomonas aeruginosa* isolation, as well. At day 32 after the institution of inhaled colistin a culture consisting of normal flora was obtained. Bronchoconstriction was not observed at anytime during treatment. The infection was cured and the child was extubated and discharged from the ICU.

Case 3

Case 3 was a 4-year-old female with no underlying disease who was admitted in the ICU with acute respiratory distress syndrome due to thermal burn of the airway requiring tracheostomy. The child received a variety of intravenous antibiotics before the administration of inhaled colistin because of 3 episodes of septicemia due to *Pseudomonas aeruginosa*, *Escherichia coli* and *Staphylococcus* coagulase negative. *Pseudomonas aeruginosa* septicemia was treated successfully with intravenous colistin. *Pseudomonas aeruginosa* was also isolated from cultures of tracheobronchial

secretions. The susceptibility pattern of this isolate is presented in the Table. However, due to the observed clinical picture of tracheobronchitis and the persistence of a high microbial load of *Pseudomonas aeruginosa* in tracheobronchial secretions (>100.000 cfu/ml), inhaled colistin alone was administered at a dosage of 75 mg diluted in 3 ml of normal saline twice daily for 15 days (a daily dosage of 1.875.000 IU of colistin, administered in 2 divided doses). At day 11 of the administration of inhaled colistin a culture of tracheobronchial secretions consisting of normal flora was obtained. Bronchoconstriction, attributed to the tracheobronchitis, was present before the initiation of inhaled colistin and was unsuccessfully treated with bronchodilators (specifically, salbutamol, ipratropium). Bronchoconstriction did not worsen during treatment. The child recovered from the infection but could not overcome the need for permanent tracheostomy and tracheal dilatations.

Discussion

We report a case series of pediatric critically ill population who received inhaled colistin for the treatment of tracheobronchitis (2 children) and pneumonia (1 infant). Case 1 and 3 of tracheobronchitis were caused by *Pseudomonas aeruginosa*, while case 1 was co-infected with a multi-drug resistant *Acinetobacter baumannii* isolate. The infection, in both these two cases, was cured with the administration of inhaled colistin alone. The case of pneumonia was caused by *Pseudomonas aeruginosa*. This infection was treated concurrently with intravenous antibiotics depending on susceptibility results for the 2/3 of the total duration of inhaled colistin treatment. The outcome was cure for this case also. Bacteriological eradication of the responsible pathogen was confirmed by quantitative cultures of tracheobronchial secretions in all 3 cases.

The rationale justifying the choice of inhaled colistin or other appropriate inhaled antibiotics as monotherapy for the treatment of patients with tracheobronchitis is that tracheobronchitis represents a topical inflammatory process that could be controlled with locally administered antibiotics.¹² A placebo-controlled study in critically ill patients with ventilator-associated tracheobronchitis (VAT) showed that inhaled antibiotics decreased the signs of respiratory infection and the use of systemic antibiotics.²¹ In our cases the only active antibiotic agent for inhalation was colistin

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

176 based on the in vitro susceptibility pattern of the isolates. In addition, based on
177 preliminary evidence, adjunctive inhaled colistin to intravenous antibiotic treatment
178 improved the outcome of pneumonia.^{17,22} On this ground, inhaled colistin was selected
179 as a therapeutic regimen for case 2.

180
181 The dosage administered to the 3 children presented in our study was 75mg of
182 colistimethate sodium diluted in 3 ml of normal saline, twice daily. This equals to a
183 daily dosage 1.875.000 IU of colistin, administered in two divided doses. According to
184 the national formulary, the recommended dosage of inhaled colistimethate sodium for
185 children older than 2 years and adults with cystic fibrosis is 1-2.000.000 IU, 2-3 times a
186 day. Regarding the 7.5-month-old infant in our report, the dosage of the 1.875.000 IU
187 per day was chosen due to her critical condition. All 3 children were closely monitored
188 for adverse events. No adverse event related to colistin treatment was noted in our cases.

189
190 In order to achieve the most of the benefits conferred by inhaled antibiotics in
191 mechanical ventilated patients several conditions should be met. The device used for
192 inhalation (nebulizer), the ventilator and the ventilator circuit, the inhaled agent and
193 patient characteristics are aspects of major significance. Nebulizers are placed at a
194 distance from the endotracheal tube in the inspiratory limb of the ventilator circuit and
195 their deliverance of small particles of the drug is achieved at the maximum with high
196 gas pressure and flow and low humidity as well as low gas density. In addition,
197 nebulizers should be operated intermittently to avoid waste of the drug during
198 exhalation time. Recently, a new electronic nebulizer the Pulmonary Drug Delivery
199 System (PDDS) utilizes information from a pressure sensor to generate the aerosol
200 during a specific time of the respiratory circle and that leads to delivery of the 50-70%
201 of the nominal dose of the drug.²³ Patient related factors such as severity of airway
202 obstruction if any, dynamic hyperinflation of the lung and synchronization with the
203 ventilator are important for drug delivery, as well. Specifically, evidence from published
204 studies suggests that colistin can be successfully nebulized with more than one of the
205 commercially available nebulizers.²⁴

One fact of major importance in all three cases is that the adjunctive use of inhaled colistin or inhaled colistin alone succeeded in the reduction and finally the total elimination of the microbial load in respiratory secretions. When treating vulnerable pediatric patients, issues of safety are of major concern. The administration of inhaled colistin minimizes the risk of systemic adverse events. On the contrary, the main worry of physicians regarding inhaled colistin is the provocation of serious bronchoconstriction.^{25,26} However, even though bronchoconstriction pre-existed in 2 of our cases, it did not deteriorate with the initiation of inhaled colistin.

In conclusion, inhaled colistin was effective for the treatment of two children with tracheobronchitis and one infant with necrotizing pneumonia, while no adverse events were observed. Accumulating data on inhaled colistin use in the adult critical care population support its safety profile. This may provide the ground for further research in the pediatric critical care setting regarding inhaled colistin and its use in pediatric patients without cystic fibrosis.

Reference list

1. Hagerman JK, Knechtel SA, Klepser ME. Tobramycin solution for inhalation in cystic fibrosis patients: a review of the literature. *Expert Opin Pharmacother* 2007;8:467-75.
2. Lenoir G, Antypkin YG, Miano A, et al. Efficacy, safety, and local pharmacokinetics of highly concentrated nebulized tobramycin in patients with cystic fibrosis colonized with *Pseudomonas aeruginosa*. *Paediatr Drugs* 2007;9 Suppl 1:11-20.
3. Ratjen F, Rietschel E, Kasel D, et al. Pharmacokinetics of inhaled colistin in patients with cystic fibrosis. *J Antimicrob Chemother* 2006;57:306-11.
4. Kaplan JE, Benson C, Holmes KH, Brooks JT, Pau A, Masur H. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep* 2009;58:1-207; quiz CE1-4.
5. Checchia P. Identification and management of severe respiratory syncytial virus. *Am J Health Syst Pharm* 2008;65:S7-12.

- 238 6. Eiland LS, Eiland EH. Zanamivir for the prevention of influenza in adults and
239 children age 5 years and older. *Ther Clin Risk Manag* 2007;3:461-5.
- 240 7. LaForce C, Man CY, Henderson FW, et al. Efficacy and safety of inhaled zanamivir
241 in the prevention of influenza in community-dwelling, high-risk adult and adolescent
242 subjects: a 28-day, multicenter, randomized, double-blind, placebo-controlled trial. *Clin*
243 *Ther* 2007;29:1579-90; discussion 1577-8.
- 244 8. Brochet MS, McDuff AC, Bussieres JF, et al. Comparative efficacy of two doses of
245 nebulized colistimethate in the eradication of *Pseudomonas aeruginosa* in children with
246 cystic fibrosis. *Can Respir J* 2007;14:473-9.
- 247 9. Hodson ME, Gallagher CG, Govan JR. A randomised clinical trial of nebulised
248 tobramycin or colistin in cystic fibrosis. *Eur Respir J* 2002;20:658-64.
- 249 10. Marchetti F, Giglio L, Candusso M, Faraguna D, Assael BM. Early antibiotic
250 treatment of *pseudomonas aeruginosa* colonisation in cystic fibrosis: a critical review of
251 the literature. *Eur J Clin Pharmacol* 2004;60:67-74.
- 252 11. Reed MD, Stern RC, O'Riordan MA, Blumer JL. The pharmacokinetics of colistin
253 in patients with cystic fibrosis. *J Clin Pharmacol* 2001;41:645-54.
- 254 12. Agrafiotis M, Siempos I, Falagas ME. Frequency, prevention, outcome, and
255 treatment of ventilator-associated tracheobronchitis: systematic review and meta-
256 analysis. *Respir Med* 2010;104:325-36.
- 257 13. Cook DJ, Walter SD, Cook RJ, Griffith LE, Guyatt GH, Leasa D, et al. Incidence of
258 and risk factors for ventilator-associated pneumonia in critically ill patients. *Ann Intern*
259 *Med*. 1998;129:433-40
- 260 14. Falagas ME, Kasiakou SK, Tsiodras S, Michalopoulos A. The use of intravenous
261 and aerosolized polymyxins for the treatment of infections in critically ill patients: a
262 review of the recent literature. *Clin Med Res* 2006;4:138-46.
- 263 15. Falagas ME, Siempos, II, Rafailidis PI, Korbila IP, Ioannidou E, Michalopoulos A.
264 Inhaled colistin as monotherapy for multidrug-resistant gram (-) nosocomial
265 pneumonia: a case series. *Respir Med* 2009;103:707-13.
- 266 16. Horianopoulou M, Lambropoulos S, Papafragas E, Falagas ME. Effect of
267 aerosolized colistin on multidrug-resistant *Pseudomonas aeruginosa* in bronchial
268 secretions of patients without cystic fibrosis. *J Chemother* 2005;17:536-8.

- 1
2
3
4
5 269 17. Korbila IP, Michalopoulos A, Rafailidis PI, Nikita D, Samonis G, Falagas ME.
6 270 Inhaled colistin as adjunctive to intravenous colistin for the treatment of
7
8 271 microbiologically documented VAP: a comparative cohort study. Clin Microbiol Infect
9
10 272 2009.
11
12 273 18. Michalopoulos A, Kasiakou SK, Mastora Z, Rellos K, Kapaskelis AM, Falagas ME.
13 274 Aerosolized colistin for the treatment of nosocomial pneumonia due to multidrug-
14 275 resistant Gram-negative bacteria in patients without cystic fibrosis. Crit Care
15
16 276 2005;9:R53-9.
17
18 277 19. Falagas ME, Sideri G, Vouloumanou EK, Papadatos JH, Kafetzis DA. Intravenous
19
20 278 colistimethate (colistin) use in critically ill children without cystic fibrosis. Pediatr
21
22 279 Infect Dis J 2009;28:123-7.
23
24 280 20. Falagas ME, Vouloumanou EK, Rafailidis PI. Systemic colistin use in children
25
26 281 without cystic fibrosis: a systematic review of the literature. Int J Antimicrob Agents
27
28 282 2009;33:503 e1- e13.
29
30 283 21. Palmer LB, Smaldone GC, Chen JJ, et al. Aerosolized antibiotics and ventilator-
31
32 284 associated tracheobronchitis in the intensive care unit. Crit Care Med 2008;36:2008-13.
33
34 285 22. Berlana D, Llop JM, Fort E, Badia MB, Jodar R. Use of colistin in the treatment of
35
36 286 multiple-drug-resistant gram-negative infections. Am J Health Syst Pharm 2005;62:39-
37
38 287 47.
39
40 288 23. Dhand R, Guntur VP. How best to deliver aerosol medications to mechanically
41
42 289 ventilated patients. Clin Chest Med 2008;29:277-96, vi.
43
44 290 24. Katz SL, Ho SL, Coates AL. Nebulizer choice for inhaled colistin treatment in
45
46 291 cystic fibrosis. Chest 2001;119:250-5.
47
48 292 25. Alothman GA, Ho B, Alsaadi MM, et al. Bronchial constriction and inhaled colistin
49
50 293 in cystic fibrosis. Chest 2005;127:522-9.
51
52 294 26. Cunningham S, Prasad A, Collyer L, Carr S, Lynn IB, Wallis C.
53
54 295 Bronchoconstriction following nebulised colistin in cystic fibrosis. Arch Dis Child
55
56 296 2001;84:432-3.
57
58
59
60

Table. Characteristics and outcomes of critically ill children without cystic fibrosis who received inhaled colistin (colistimethate sodium) for the treatment of tracheobronchitis and pneumonia.

	Patient 1	Patient 2	Patient 3
Age	10y	7.5mo	4y
Sex	M	F	F
Underlying disease	ADEM	None	None
Reason for ICU admission	Encephalomyelitis	Septic shock, necrotizing pneumonia	Respiratory burn, respiratory distress
Length of stay (LOS) in the ICU	≈7mo	≈1.5mo	≈3mo
Length of time on the ventilator	≈1.5mo (followed by tracheostomy)	≈1.5mo	11d (followed by tracheostomy)
Type of infection	Tracheobronchitis	Necrotizing pneumonia	Tracheobronchitis
Isolated pathogen(s)	<i>Acinetobacter baumannii</i> , <i>Pseudomonas aeruginosa</i>	<i>Pseudomonas aeruginosa</i>	<i>Pseudomonas aeruginosa</i>
Site of isolation	Bronchial culture	Bronchial culture	Bronchial culture
Susceptibility pattern of the isolated pathogen(s)	<i>Acinetobacter baumannii</i> Amoxicillin-clavulanic acid: S, minocycline: I, doxycycline: I, colistin: S <i>Pseudomonas aeruginosa</i> Piperacillin: S, ciprofloxacin: S, ticarcillin-clavulanate: S, aztreonam: S, piperacillin-tazobactam: S, imipenem: S, gentamicin: R, tobramycin: R, netilmicin: R, colistin: S	<i>Pseudomonas aeruginosa</i> Piperacillin: S, piperacillin-tazobactam: S, cefotaxime: R, aztreonam: S, imipenem: S, ciprofloxacin: S, gentamicin: I, tobramycin: I, netilmicin: I, colistin: S	<i>Pseudomonas aeruginosa</i> Piperacillin: S, piperacillin-tazobactam: S, ticarcillin-clavulanate: S, cefotaxime: R, aztreonam: S, ciprofloxacin: S, gentamicin: I, tobramycin: I, netilmicin: I, colistin: S
Prior administration of intravenous colistin	Yes*	No	Yes**
Concomitant antibiotic treatment to inhaled colistin	None	iv (piperacillin-tazobactam plus gentamicin for 10d, meropenem plus vancomycin for the following 11d)	None
Time of institution of inhaled colistin	Day 206 after ICU admission (while on tracheostomy)	Day 3 after ICU admission (while on intubation)	Day 27 after ICU admission (while on tracheostomy)
Dosage of inhaled colistin	75mg diluted in 3ml of normal saline twice daily	75mg diluted in 3ml of normal saline twice daily	75mg diluted in 3ml of normal saline twice daily
Duration of treatment with inhaled colistin	25d	32d	15d

Delivery of inhaled colistin	Via a nebulizer apparatus connected to the tracheostomy circuit		Via a nebulizer apparatus connected to the ventilation system		Via a nebulizer apparatus connected to the tracheostomy circuit	
Type of ventilator	Siemens Servo-i Ventilator [#]		Siemens Servo-i Ventilator ^{##}		Siemens Servo-i Ventilator [#]	
Humidification	On		On		On	
Quantitative change of the microbial burden of the isolated pathogen(s) (cfu/ml)/Days after institution of inhaled colistin	<i>Acinetobacter baumannii</i>		<i>Pseudomonas aeruginosa</i>		<i>Pseudomonas aeruginosa</i>	
	Day 1	>100000	1 day prior to colistin institution	>100000	Day 1	>100000
	Day 4	95000	Day 3	100000	Day 4	80000
	Day 11	75000	Day 10	75000	Day 8	Rare microbes found
	Day 17	Rare microbes found	Day 16	70000	Day 11	Natural flora
	Day 21	Natural flora	Day 28	5000		
			Day 32	Natural flora		
	<i>Pseudomonas aeruginosa</i>					
	Day 1	>100000				
	Day 4	75000				
	Day 11	45000				
	Day 17	6000				
	Day 21	Natural flora				
Outcome	Cured from the infection		Cured from the infection		Cured from the infection	
	Discharged from the ICU/still with tracheostomy-no colonization		Discharged from the ICU		Discharged from the ICU/still with tracheostomy-no colonization	
Adverse events						
Nephrotoxicity	No		No		No	
Urea/creatinine [‡] (before colistin treatment–after colistin treatment)	(23/0.7–25/0.6)		(47/7–15/0.3)		(30/0.5–35/0.5)	
Other toxicity	No		No		No	

Abbreviations: F: female, M: male, ADEM: Acute disseminated encephalomyelitis, y: year(s), mo: month(s), d: days, S: susceptibility, I: intermediate susceptibility, R: resistant, iv: intravenous.

[‡]: mg/dl

^{*}: Administered for the treatment of *Acinetobacter baumannii* bacteremia.

^{**}: Administered for the treatment of *Pseudomonas aeruginosa* bacteremia.

[#]: Prior to colistin treatment.

^{##}: While on colistin treatment.