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4 **1 Inhaled colistin for the treatment of tracheobronchitis and pneumonia**
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6 **2 in critically ill children without cystic fibrosis**
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10 Matthew E. Falagas^{1,2,3}, MD, MSc, DSc, Georgia Sideri⁴, MD, Ioanna P. Korbila¹, MD,
11 Evridiki K. Vouloumanou¹, MD, John H. Papadatos⁴, MD, PhD,
12 Dimitris A. Kafetzis⁵, MD, PhD
13
14
15
16
17

18 1. Alfa Institute of Biomedical Sciences (AIBS), Athens, Greece

19 2. Department of Medicine, Henry Dunant Hospital, Athens, Greece

20 3. Department of Medicine, Tufts University School of Medicine, Boston,
21 Massachusetts, USA

22 4. Pediatric Intensive Care Unit, P. & A. Kyriakou Children's Hospital, Athens, Greece

23 5. Second Department of Pediatrics, University of Athens, P. & A. Kyriakou Children's
24 Hospital, Athens, Greece
25
26
27
28
29
30
31

32 **Corresponding author:** Matthew E. Falagas, MD, MSc, DSc

33 Alfa Institute of Biomedical Sciences (AIBS),

34 9 Neapoleos Street, 151 23 Marousi, Greece

35 Tel: +30 (694) 611-0000,

36 Fax: +30 (210) 683-9605

37 E-mail: m.falagas@aibs.gr
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29 **Abstract**

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

46
47 **Keywords:** Gram-negative infections, polymyxins, *Pseudomonas*, *Acinetobacter*,
48 intensive care unit

49 Introduction

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

59
60 The strategy of antimicrobial drug delivery through inhalation has been tested in adult
61 and children population. Specifically, regarding colistin, several studies in adult and
62 pediatric patients with cystic fibrosis have investigated the role of inhaled colistin to
63 eradicate *Pseudomonas aeruginosa*, which chronically colonizes the respiratory tract, as
64 well as its adverse events.⁸⁻¹¹ **Patients on mechanical ventilation constitute a high-risk**
65 **group for difficult-to-treat respiratory infections, including both ventilator -associated**
66 **tracheobronchitis (VAT) and ventilator-associated pneumonia (VAP).**^{12,13} Recent data
67 provide preliminary evidence of inhaled colistin's value to cure difficult-to-treat
68 infections of the respiratory tract caused by multi-drug resistant Gram-negative
69 pathogens such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Klebsiella*
70 *pneumoniae* in the intensive care unit (ICU) setting in patients without cystic fibrosis.¹⁴⁻
71 ¹⁸ On the other hand, in the field of pediatric critical care medicine there is a lack of
72 evidence regarding the role of inhaled colistin to treat such infections.^{19,20}

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

79 Case description

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5 80 Children who received inhaled colistin (colistimethate sodium) [1mg equals 12.500
6 81 international units (IU) of colistin base activity] in the ICU of the A. & P. Kyriakou
7 82 tertiary-care pediatric hospital during 2004-2009, were identified by reviewing ICU
8 83 records. Data presented in this study were extracted from medical charts. Specifically,
9 84 data regarding the demographical characteristics, underlying disease, reason for ICU
10 85 admission, length of stay in the ICU and duration of ventilation, type of infection, site
11 86 of isolation, and susceptibility pattern of each isolated pathogen, whether intravenous
12 87 colistin was administered prior to inhaled colistin, the device used to deliver inhaled
13 88 colistin, the type of the ventilator used, and presence of humidification, as well as time
14 89 of institution, dosage and duration of inhaled colistin treatment, any concomitantly
15 90 administered antibiotics, quantitative measures of the microbial load, the outcome and
16 91 any adverse event reported are presented in the Table. The collection and report of the
17 92 data presented in our study was approved from the hospital's ethical committee.
18 93 Specifically, this report on inhaled colistin constitutes a nested study within a larger one
19 94 regarding the toxicity of rarely administered (either intravenously or through inhalation)
20 95 antimicrobial agents in children.
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34 97 **Case 1**

35 98 Case 1 was a 10-year-old male suffering from acute disseminated encephalomyelitis
36 99 attributed to infection with influenza B virus. This child stayed in the ICU for 7 months
37 100 and developed 5 episodes of septicemia and 2 episodes of septic shock for which he
38 101 received various antibiotics. Polymyxin-only-susceptible *Acinetobacter baumannii* was
39 102 isolated in one blood culture, and the infection was cured with the administration of
40 103 intravenous colistin. The child had a clinical picture of tracheobronchitis, with a high
41 104 microbial load of *Acinetobacter baumannii* and *Pseudomonas aeruginosa* in cultures of
42 105 tracheobronchial secretions (the susceptibility pattern of these isolates is presented in
43 106 the Table). In this regard, inhaled colistin was administered alone at a dosage of 75mg
44 107 diluted in 3 ml of normal saline twice daily (this equals to a daily dosage of 1.875.000
45 108 IU of colistin, administered in 2 divided doses) for 25 days. At day 21 of inhaled
46 109 colistin treatment, a culture of tracheobronchial secretions with normal flora was
47 110 obtained. Bronchoconstriction, attributed to the tracheobronchitis, was present before
48 111 the initiation of inhaled colistin and was unsuccessfully treated with bronchodilators
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5 112 (specifically, salbutamol, ipratropium). Bronchoconstriction did not worsen during
6 113 treatment. The outcome of the infection was favorable. However, the child exhibited
7 114 serious neurological deficiencies that led to the need of permanent tracheostomy and
8 115 gastrostomy.
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13 Case 2

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15 118 Case 2 was a 7.5-month-old female with no underlying disease, nor immuno-
16 119 deficiencies who was admitted at the ICU with septic shock due to necrotizing
17 120 pneumonia caused by *Pseudomonas aeruginosa*, which was isolated in blood and
18 121 bronchial secretions cultures obtained at the day of admission in the ICU. The
19 122 susceptibility pattern of the *Pseudomonas aeruginosa* is presented at the Table. The
20 123 child received various intravenous antibiotic agents. Inhaled colistin was initiated 3
21 124 days after the acquisition of the index cultures at a dosage of 75 mg diluted in 3 ml of
22 125 normal saline twice daily (a daily dosage of 1.875.000 IU of colistin), administered in 2
23 126 divided doses) for 32 days. Concomitant to inhaled colistin administration of
24 127 intravenous antibiotic regimens included piperacillin/tazobactam and gentamicin for the
25 128 first 10 days of administration of colistin and meropenem plus vancomycin (due to the
26 129 isolation of *Staphylococcus coagulase-negative* from blood culture) for the following 11
27 130 days. During the course of the infection the child developed bilateral pleural effusions.
28 131 Culture of the pleural fluid led to *Pseudomonas aeruginosa* isolation, as well. At day 32
29 132 after the institution of inhaled colistin a culture consisting of normal flora was obtained.
30 133 Bronchoconstriction was not observed at anytime during treatment. The infection was
31 134 cured and the child was extubated and discharged from the ICU.
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47 Case 3

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49 137 Case 3 was a 4-year-old female with no underlying disease who was admitted in the
50 138 ICU with acute respiratory distress syndrome due to thermal burn of the airway
51 139 requiring tracheostomy. The child received a variety of intravenous antibiotics before
52 140 the administration of inhaled colistin because of 3 episodes of septicemia due to
53 141 *Pseudomonas aeruginosa*, *Escherichia coli* and *Staphylococcus coagulase negative*.
54 142 *Pseudomonas aeruginosa* septicemia was treated successfully with intravenous colistin.
55 143 *Pseudomonas aeruginosa* was also isolated from cultures of tracheobronchial
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5 144 secretions. The susceptibility pattern of this isolate is presented in the Table. However,
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7 145 due to the observed clinical picture of tracheobronchitis and the persistence of a high
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9 146 microbial load of *Pseudomonas aeruginosa* in tracheobronchial secretions (>100.000
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11 147 cfu/ml), inhaled colistin alone was administered at a dosage of 75 mg diluted in 3 ml of
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13 148 normal saline twice daily for 15 days (a daily dosage of 1.875.000 IU of colistin,
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15 149 administered in 2 divided doses). At day 11 of the administration of inhaled colistin a
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17 150 culture of tracheobronchial secretions consisting of normal flora was obtained.
18
19 151 Bronchoconstriction, attributed to the tracheobronchitis, was present before the
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21 152 initiation of inhaled colistin and was unsuccessfully treated with bronchodilators
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23 153 (specifically, salbutamol, ipratropium). Bronchoconstriction did not worsen during
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25 154 treatment. The child recovered from the infection but could not overcome the need for
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27 155 permanent tracheostomy and tracheal dilatations.
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27 157 Discussion

29 158 We report a case series of pediatric critically ill population who received inhaled
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31 159 colistin for the treatment of tracheobronchitis (2 children) and pneumonia (1 infant).
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33 160 Case 1 and 3 of tracheobronchitis were caused by *Pseudomonas aeruginosa*, while case
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35 161 1 was co-infected with a multi-drug resistant *Acinetobacter baumannii* isolate. The
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37 162 infection, in both these two cases, was cured with the administration of inhaled colistin
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39 163 alone. The case of pneumonia was caused by *Pseudomonas aeruginosa*. This infection
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41 164 was treated concurrently with intravenous antibiotics depending on susceptibility results
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43 165 for the 2/3 of the total duration of inhaled colistin treatment. The outcome was cure for
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45 166 this case also. Bacteriological eradication of the responsible pathogen was confirmed by
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47 167 quantitative cultures of tracheobronchial secretions in all 3 cases.
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49 169 The rationale justifying the choice of inhaled colistin or other appropriate inhaled
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51 170 antibiotics as monotherapy for the treatment of patients with tracheobronchitis is that
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53 171 tracheobronchitis represents a topical inflammatory process that could be controlled
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55 172 with locally administered antibiotics.¹² A placebo-controlled study in critically ill
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57 173 patients with ventilator-associated tracheobronchitis (VAT) showed that inhaled
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59 174 antibiotics decreased the signs of respiratory infection and the use of systemic
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175 antibiotics.²¹ In our cases the only active antibiotic agent for inhalation was colistin

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4 176 based on the in vitro susceptibility pattern of the isolates. In addition, based on
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6 177 preliminary evidence, adjunctive inhaled colistin to intravenous antibiotic treatment
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8 178 improved the outcome of pneumonia.^{17,22} On this ground, inhaled colistin was selected
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10 179 as a therapeutic regimen for case 2.
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13 181 The dosage administered to the 3 children presented in our study was 75mg of
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15 182 colistimethate sodium diluted in 3 ml of normal saline, twice daily. This equals to a
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17 183 daily dosage 1.875.000 IU of colistin, administered in two divided doses. According to
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19 184 the national formulary, the recommended dosage of inhaled colistimethate sodium for
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21 185 children older than 2 years and adults with cystic fibrosis is 1-2.000.000 IU, 2-3 times a
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23 186 day. Regarding the 7.5-month-old infant in our report, the dosage of the 1.875.000 IU
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25 187 per day was chosen due to her critical condition. All 3 children were closely monitored
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27 188 for adverse events. No adverse event related to colistin treatment was noted in our cases.
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30 190 In order to achieve the most of the benefits conferred by inhaled antibiotics in
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32 191 mechanical ventilated patients several conditions should be met. The device used for
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34 192 inhalation (nebulizer), the ventilator and the ventilator circuit, the inhaled agent and
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36 193 patient characteristics are aspects of major significance. Nebulizers are placed at a
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38 194 distance from the endotracheal tube in the inspiratory limb of the ventilator circuit and
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40 195 their deliverance of small particles of the drug is achieved at the maximum with high
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42 196 gas pressure and flow and low humidity as well as low gas density. In addition,
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44 197 nebulizers should be operated intermittently to avoid waste of the drug during
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46 198 exhalation time. Recently, a new electronic nebulizer the Pulmonary Drug Delivery
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48 199 System (PDDS) utilizes information from a pressure sensor to generate the aerosol
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50 200 during a specific time of the respiratory circle and that leads to delivery of the 50-70%
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52 201 of the nominal dose of the drug.²³ Patient related factors such as severity of airway
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54 202 obstruction if any, dynamic hyperinflation of the lung and synchronization with the
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56 203 ventilator are important for drug delivery, as well. Specifically, evidence from published
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58 204 studies suggests that colistin can be successfully nebulized with more than one of the
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60 205 commercially available nebulizers.²⁴
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4 207 One fact of major importance in all three cases is that the adjunctive use of inhaled
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6 208 colistin or inhaled colistin alone succeeded in the reduction and finally the total
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8 209 elimination of the microbial load in respiratory secretions. When treating vulnerable
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10 210 pediatric patients, issues of safety are of major concern. The administration of inhaled
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12 211 colistin minimizes the risk of systemic adverse events. On the contrary, the main worry
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14 212 of physicians regarding inhaled colistin is the provocation of serious
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16 213 bronchoconstriction.^{25,26} However, even though bronchoconstriction pre-existed in 2 of
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18 214 our cases, it did not deteriorate with the initiation of inhaled colistin.
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21 216 In conclusion, inhaled colistin was effective for the treatment of two children with
22 217 tracheobronchitis and one infant with necrotizing pneumonia, while no adverse events
23 218 were observed. Accumulating data on inhaled colistin use in the adult critical care
24 219 population support its safety profile. This may provide the ground for further research
25 220 in the pediatric critical care setting regarding inhaled colistin and its use in pediatric
26 221 patients without cystic fibrosis.

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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

1					
2					
3	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	
4					
5	Type of ventilator	Siemens Servo-i Ventilator [#]	Siemens Servo-i Ventilator ^{##}	Siemens Servo-i Ventilator [#]	
6					
7	Humidification	On	On	On	
8					
9	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>	
10		Day 1 >100000	1 day prior to colistin institution >100000	Day 1 >100000	
11		Day 4 95000	Day 3 100000	Day 4 80000	
12		Day 11 75000	Day 10 75000	Day 8 Rare microbes found	
13					
14		Day 17 Rare microbes found	Day 16 70000	Day 11 Natural flora	
15		Day 21 Natural flora	Day 28 5000		
16			Day 32 Natural flora		
17		<i>Pseudomonas aeruginosa</i>			
18		Day 1 >100000			
19		Day 4 75000			
20		Day 11 45000			
21		Day 17 6000			
22		Day 21 Natural flora			
23	Outcome	Cured from the infection	Cured from the infection	Cured from the infection	
24		Discharged from the ICU/still with tracheostomy-no colonization	Discharged from the ICU	Discharged from the ICU/still with tracheostomy-no colonization	
25					
26	Adverse events				
27	Nephrotoxicity	No	No	No	
28					
29	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)	
30					
31	Other toxicity	No	No	No	
32					

44

45 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.

46 ‡: mg/dl

47

48 *: Administered for the treatment of *Acinetobacter baumannii* bacteremia.

49

50 **: Administered for the treatment of *Pseudomonas aeruginosa* bacteremia.

51

52 #: Prior to colistin treatment.

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54 ##: While on colistin treatment.

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