The Use of Intravenous and Aerosolized Polymyxins for the Treatment of Infections in Critically Ill Patients: A Review of the Recent Literature

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Intravenous and aerosolized polymyxins are being used increasingly, especially in the critical care setting, for treating patients with infections due to multidrug-resistant Gram-negative bacteria, mainly *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. Recent literature suggests that intravenous colistin and polymyxin B have acceptable effectiveness for the treatment of patients with bacteremia, as well as infections of various systems and organs, including pneumonia, bacteremia, skin and soft tissue, and urinary tract infections. Although data from recent studies have suggested that the toxicity of intravenous polymyxins is probably less than reported in the older literature, caution should be taken to monitor the renal function of patients who receive these antibiotics.

Keywords: *Acinetobacter*; Colistin; Inhalation; Intensive care unit; *Klebsiella*; Multidrug-resistant Gram-negative bacteria; Nebulization; Pneumonia; Polymyxin B; *Pseudomonas*; Ventilator-associated

The lack of development of new antimicrobial agents, in combination with the emergence of Gram-negative bacteria that produce extended spectrum β -lactamases and metallo- β -lactamases, represent major health threats that affect patient outcomes, particularly in the intensive care unit. Strains of *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* that exhibit resistance to almost all available antibiotics, except polymyxins, have emerged as common causes of hospital acquired infections in critically ill patients.¹⁻³ Polymyxins have been recently considered as last therapeutic options for the treatment of patients with these types of infections. In addition, the administration of polymyxins intrathecally or intraventricularly has been evaluated recently as a potential alternative intervention for the treatment of multidrug-resistant Gram-negative central nervous system infections. Although the level of evidence to support the use of polymyxins by these modes of administration is low, the reported data are promising.⁴⁻⁶

History, Mechanism of Action and Spectrum of Activity

Polymyxins are a group of polypeptide cationic antibiotics.⁷ Major components of this class of antimicrobial agents that

have been used in clinical practice represent colistin (polymyxin E) and polymyxin B. Colistin and polymyxin B were discovered from different species of *Bacillus polymyxa* in the 1940s and were extensively used parenterally for approximately two decades, after which they were gradually withdrawn from clinical practice owing to reports of toxicity.⁸⁻¹² Specifically, several studies that assessed the safety of parenteral polymyxins reported frequent development of renal and neurological adverse effects.^{13,14} In addition, numerous case reports published in the 1960s and 1970s associated the administration of polymyxins with the development of acute renal failure.¹⁵⁻¹⁷

Polymyxins consist of a cyclic decapeptide molecule, which is positively charged and linked to a fatty acid chain that has been found to be either 6-methyl-octanoic acid or 6-methyl-eptanoic acid. The main difference between the molecules of polymyxin B and colistin is in the amino acid components.⁷ Colistin consists of D-leucine, L-threonine and L- α -diaminobutyric acid, while polymyxin B contains D-phenylalanine instead of D-leucine.⁷ The cationic molecules of polymyxin B and colistin compete and displace Ca^{2+} and Mg^{2+} ions which normally stabilize the lipopolysaccharide molecule of the outer membrane of Gram-negative bacteria. This

outer membrane of Gram-negative bacteria. This displacement causes local disturbance of the cell membrane, increased cell permeability, leakage of the cell content, cell lysis and death.^{18,19} In addition, a remarkable property of polymyxins is the ability to neutralize lipopolysaccharide molecules of Gram-negative bacteria, thus inducing anti-endotoxin activities.²⁰ In patients with sepsis, continuous hemodialysis therapy with polymyxin-B immobilized fiber has been correlated with improvement of the survival rates.²¹ Their spectrum of activity includes Gram-negative aerobic bacilli only, including *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Klebsiella* species, *Enterobacter* species, *Salmonella* species, *Shigella* species and *Escherichia coli*. *Stenotrophomonas maltophilia* strains are usually susceptible to polymyxins.^{22,23} On the other hand *Proteus* species, *Serratia* species, *Burkholderia* species, *Providencia* species and *Edwardsiella* spp. are resistant to polymyxins.²²

Dosage and Pharmacokinetic/Pharmacodynamic Properties

Two forms of colistin are commercially available for clinical use: 1) colistin sulfate that is usually used topically or orally for selective bowel decontamination, and 2) colistimethate sodium that is used parenterally. Polymyxin B is commercially available as polymyxin B sulfate.

The dosage of intravenous colistin base recommended by the manufacturer in the United States is 2.5–5 mg/kg per day divided into 2 to 4 equal doses. It should be noted that the formulation of colistin manufactured in the U.S. by Parkdale Pharmaceuticals Inc. (Rochester, MI) and distributed by Monarch Pharmaceuticals Inc. (Bristol, TN) contains 150 mg colistin base.²⁴ Dosage adjustments are recommended for patients with mild to moderate renal dysfunction. Specifically, when the serum creatinine level is 1.3–1.5 mg/dl, 1.6–2.5 mg/dl or ≥ 2.6 mg/dl, the recommended dosage of intravenous colistin for serious infections is 2 million IU every 12 hours, 24 hours or 36 hours, respectively. In the United Kingdom, a dosing regimen of 4–6 mg/kg (50,000–75,000 IU/kg) of colistimethate sodium per day in 3 divided doses is recommended for adults and children with normal renal function and body weight ≤ 60 kg, and 240–480 mg (3–6 million IU) per day in 3 divided doses for those with body weight >60 kg. This formulation, which is manufactured by Alpharma A/S (Copenhagen, Denmark) and distributed by Forest Laboratories (Kent, United Kingdom) contains 80 mg of colistimethate sodium (1 mg of colistimethate sodium is equal to 12,500 IU).²⁵ To avoid confusion regarding dosing of colistin, it is preferable to use a dosing system based on International Units (IU). Pure colistin base has a potency of 30,000 IU/mg. The dosage of intravenous polymyxin B recommended by the manufacturer is 1.5–2.5 mg/kg/day (15,000–25,000 IU/kg/day), divided into 2 equal doses for adults and children older than 2 years with normal renal function. One milligram of polymyxin B is equal to 10,000 IU.²⁶ Recommendations for dosage adjustment of polymyxin B in the presence of renal impairment have not been well established. For both regimens, there are no dosage

adjustments for patients with liver failure. It should be noted that neurotoxicity, including neuromuscular blockade and apnea, has been observed with high doses of colistimethate sodium administered intravenously, and it more commonly presents in patients with renal dysfunction when the dosage is not adjusted.

The dosage of aerosolized colistimethate sodium recommended in the United Kingdom is 40 mg (500,000 IU) every 12 hours for patients with body weight ≤ 40 kg, and 80 mg (1 million IU) every 12 hours for patients with a body weight >40 kg. For recurrent pulmonary infections, the dosage can be increased to 160 mg (2 million IU) every 8 hours.²⁷

The precise pharmacokinetic-pharmacodynamic properties of polymyxin B and colistimethate sodium have not been completely clarified, and most of the available literature was published approximately three decades ago. However, both polymyxins are poorly absorbed by the gastrointestinal tract following oral administration and are eliminated by the renal route. No hepatic excretion of polymyxin B and colistimethate sodium has been reported in humans.²⁸ Both polymyxins have rapid concentration dependent bactericidal activity against Gram-negative pathogens²⁹ and exhibit considerable post-antibiotic effects at high concentrations.^{28,30}

Intravenous Polymyxins in Critically Ill Patients

No well-designed, randomized controlled trials (phase II or III trials) have been conducted to comprehensively evaluate the effectiveness and safety of polymyxins for the treatment of Gram-negative bacterial infections and to elucidate their clinical indications. However, the need for their use in patients with infections caused by polymyxin-only susceptible microorganisms or with infections where the available antimicrobial therapeutic options have failed, has led to the accumulation of valuable experience regarding their usefulness.

Table 1 (pages 140–142) summarizes recently published studies that assessed the effectiveness and safety of parenteral polymyxin B and colistimethate sodium for the treatment of critically ill patients with multidrug-resistant Gram-negative bacterial infections. Both medications have been used parenterally in cases of pneumonia, bacteremia, urinary tract infections, surgical site infections, abdominal infections, skin and central nervous system infections. Most recently published studies included severely ill patients with Acute Physiology and Chronic Health Evaluation II (APACHE II) scores ranging from 13 to 26 who suffered from infections caused by multidrug-resistant or polymyxin-only-susceptible Gram-negative bacteria. The observed frequency of clinical cure among patients in these studies was promising. However, a major limitation observed in most of these studies is that combinations of colistimethate sodium and polymyxin B with other antimicrobial agents were used due to the severity of the infections in the intensive care

Table 1. Characteristics and treatment outcomes of recently reported studies of critically ill patients who received intravenous polymyxins for infections due to multidrug-resistant Gram-negative bacteria.

Ref #	Setting	Number of patients	Demographics/ APACHE II score	Medication used	Duration/dosage of colistin*	Sites of infection	Pathogen	Mortality rates	Clinical cure by infection type	Definition of nephrotoxicity	Nephrotoxicity†
47	Abdominal organ transplant ICU	23 pts	Age (median): 52 y	CMS	Median duration (range): 17d (7-36d)	Pneumonia 18 cases Bacteremia 8 cases Wound 3 cases Intra-abdominal 6 cases Endocarditis 1 case Multiple types 5 cases	<i>P. aeruginosa</i>	In-hospital mortality 14 pts (61%)	Pneumonia 10/15 pts Intra-abdominal 5/6 pts Wound 1/3 pts	RF was defined by a requirement either for intermittent hemodialysis or for continuous venous hemofiltration	1/2 pts developed RF requiring artificial kidney support (the other 21 patients were already receiving artificial kidney support)
48	ICU	24 pts with sepsis/ 26 episodes of infection	Mean age: 44.3 y Mean APACHE II: 20.6	CMS	Median duration (range): 13.5 d (4-24 d) Dosage: 3 MIU q8h	VAP 15 cases (58%) Catheter-related sepsis 3 cases (12%) Empyema thoracic 1 case (4%) Post-traumatic meningitis 1 case (4%) Sinusitis 1 case (4%) UTI 1 case (4%) Sepsis of unknown primary origin 4 cases (15%)	20 cases <i>P. aeruginosa</i> (77%) 6 cases <i>A. baumannii</i> (23%)	30-day mortality 42%	VAP 11/15 cases Catheter-related sepsis 2/3 cases Empyema thoracic 0/1 case Post-traumatic meningitis 1/1 case Sepsis of unknown primary origin 3/4 cases	RF was defined as an increase in serum creatinine >1mg/dl during treatment	3 pts (14.3%). Only 1 pt required continuous venous hemodialysis
49	ICU (52%) -transplant unit (13%) -surgical and medical wards (35%)	59 pts/60 nosocomial infections	Mean age ± SD: 42.1 ± 21.4 y Mean APACHE II: 13.1	CMS	Mean duration ± SD: 12.6 ± 6.8 d Mean daily dose ± SD: 152.8 ± 62.8 mg	Pneumonia 20 pts (33%) UTI 12 pts (20%) Primary bloodstream infection 9 pts (15%) CNS infection 5 pts (8%) Surgical site 5 pts (8%) Peritonitis 4 pts (7%) Catheter-related infection 4 pts (7%) Otitis media 1 pt (2%)	39 <i>A. baumannii</i> (65%) 21 <i>P. aeruginosa</i> (35%)	22 pts (37%)	Pneumonia 5/20 cases UTI 10/12 cases Primary bloodstream infection 7/9 cases CNS infection 4/5 cases Surgical site 3/5 cases Peritonitis 2/4 cases Catheter-related infection 3/4 cases Otitis media 1/1 case	NA (information about creatinine values are provided)	22 pts (37%). 11/41 (27%) pts with normal baseline renal function had worsening during treatment (mean increase 0.9 ± 0.6). 11/19 pts (58%) with abnormal baseline renal function had worsening during treatment (mean increase 1.5 ± 1.4).
34	ICU	21 pts colistin group (CO) 14 pts imipenem group (IM)	Mean age ± SD: CO group 56.9 ± 13.1 y IM group 64.5 ± 11 y Mean APACHE II ± SD: CO group 19.6 ± 7.2 IM group 20.5 ± 7	CMS	Mean duration ± SD: CO group 14.7 ± 4.1 d IM group 13.2 ± 4.2 d	VAP	21 <i>A. baumannii</i> susceptible to colistin – CO group 14 <i>A. baumannii</i> susceptible to imipenem – IM group	In-hospital mortality: 13/21 pts CO group (62%) 9/14 pts IM group (64%) VAP-related mortality: 8/21 pts CO group (38%) 5/14 pts IM group (35.7%)	CO group: 12/21 pts IM group: 8/14 pts	In patients with normal renal function (cr. < 1.2) – RF was defined as cr. value > 2mg/dl as a reduction of cr. clearance of 50% relative to antibiotic initiation or need for RRT. In patients with abnormal renal function, RF was defined as increase of 50% of the baseline cr. level, as a reduction of cr. clear. of 50% relative to antibiotic initiation, or need for RRT	CO group: 5/21 pts (24%) IM group: 6/14 pts (42%)

Table 1. Continued

Ref #	Setting	Number of patients	Demographics/ APACHE II score	Medication used	Duration/dosage of colistin*	Sites of infection	Pathogen	Mortality rates	Clinical cure by infection type†	Definition of nephrotoxicity	Nephrotoxicity‡
31	ICU (80%) - medical, surgical wards (20%)	50 pts/ 54 episodes	Mean age ± SD: 59.2 ± 17.7 y Mean APACHE II ± SD: 16.1 ± 6.1	CMS	Mean daily dose ± SD: 4.5 ± 2.3 MIU Mean duration ± SD: 21.3 ± 16 d	Pneumonia 18 episodes (33%) Bacteremia 15 episodes (28%) Urinary tract infection 6 episodes (11%) Intra-abdominal infection 6 episodes (11%) Meningitis 3 episodes (6%) Catheter-related infection 2 episodes (4%) Surgical site infection 2 episodes (4%) Skin and subcutaneous tissue infection 1 episode (2%) Not found 1 episode (2%)	28 <i>A. baumannii</i> (52%) 23 <i>P. aeruginosa</i> (43%) 2 <i>K. pneumoniae</i> (4%) 1 Not found (2%)	In-hospital mortality 12/50 pts (24%)	Pneumonia 10/18 episodes Bacteremia 9/15 episodes Urinary tract infection 6/6 episodes Abdominal infection 5/6 episodes Meningitis 2/3 episodes Surgical site infection 1/2 episodes Catheter-related infection 2/2 episodes Skin – subcutaneous tissue infection 1/1 episode Not found 0/1 episode	RF was defined as an increase more than 50% of the baseline creatinine level to a value higher than 1.3 mg/dl or as a decline in renal function requiring renal replacement therapy	4/50 pts (8%)
2	ICU	43 pts	Mean age ± SD: 56.5 ± 16.2 y Mean APACHE II ± SD: 25.8 ± 3.7	CMS	Dosage: 3 MIU q8h Mean duration ± SD: 18.6 ± 5.8 d	Pneumonia (VAP) 21 pts Bacteremia 11 pts Pneumonia and bacteremia 3 pts Pneumonia and catheter-related infection 3 pts Pneumonia and UTI 2 pts Pneumonia and surgical wound infection 2 pts Sinusitis 1 pt	35 <i>P. aeruginosa</i> (81%) 8 <i>A. baumannii</i> (19%)	In-hospital mortality 12/43 pts (28%)	32/43 pts (74%)	Acute renal failure was defined as a rise of ≥ 2 mg/dL in serum creatinine level in patients with previously normal renal function. In patients with a history of renal insufficiency, acute on chronic renal failure was defined as at least doubling of the baseline serum creatinine level (defined as the creatinine level at the initiation of colistin treatment).	8/43 pts (18.6%)
3	ICU	55 pts colistin group (CO) 130 pts Non-colistin group (Non-CO)	Mean age ± SD: CO group 40 ± 16 y Non-CO group 41 ± 16 y Mean APACHE II ± SD: CO group 21 ± 7 Non-CO group 20 ± 7	CMS		CO group: VAP 29 pts Primary bacteremia 9 pts UTI 10 pts Other infections 7 pts Non-CO group: VAP 86 pts Primary bacteremia 25 pts UTI 11 pts Other infections 8 pts	CO group: 19 <i>P. aeruginosa</i> 36 <i>A. baumannii</i> Non-CO group: 61 <i>P. aeruginosa</i> 69 <i>A. baumannii</i>			Renal failure was defined as a serum creatinine value of 2 mg/dl or higher, as a reduction in creatinine clearance of 50% compared to therapy initiation or as a decline in renal function that prompted renal replacement therapy	NA

Table 1. Continued

Ref #	Setting	Number of patients	Demographics/ APACHE II score	Medication used	Duration/dosage of colistin*	Sites of infection	Pathogen	Mortality rates	Clinical cure by infection type	Definition of nephrotoxicity	Nephrotoxicity†
50	ICU	14 pts	Mean age: 49 y	CMS	Dosage: 2 MIU q8h Mean duration: 12 d	VAP 10 pts VAP and bacteremia 2 pts VAP and surgical site infection 2 pts	<i>A. baumannii</i>	7/14 pts (50%)	9/14 pts (64%)	NA	1 pt had deterioration of renal function (creatinine up to 2.8 mg/dl).
51	Mainly ICU pts	17 pts/19 courses	Median age: 51 y Median APACHE II: 14	CMS	Mean $\pm$ SD daily dose: 4.4 MIU (352 mg) $\pm$ 2.1 MIU (168 mg) Mean $\pm$ SD duration: 43.4 $\pm$ 14.6 d	Pneumonia 13/19 courses Bacteremia 1/19 courses UTI 2/19 courses Meningitis 2/19 courses Surgical site infection 1/19 courses	5 <i>A. baumannii</i> (25%) 12 <i>P. aeruginosa</i> (60%) 2 <i>Klebsiella pneumoniae</i> (10%) 1 <i>Enterobacter cloacae</i> (5%)	7/17 pts (41%)	14/19 courses (74%)	Renal failure was defined as an increase more than 50% of the baseline creatinine level to a value higher than 1.3 mg/dl or as a decline in renal function requiring renal replacement therapy	Median baseline serum creatinine = 0.6 mg/dl. Slight increase of the median of values of creatinine at the end by 0.1 mg/dl. Median baseline BUN = 42 mg/dl. Median final BUN 41 mg/dl. 1 pt had an increase of more than 50% of the baseline creatinine level to a value higher than 1.3 mg/dl at the end of colistin treatment.
52	ICU (92%)	25 pts/29 courses [21 courses IV, 6 courses aerosol, 2 courses combination]	Mean age: 55 y Mean APACHE II: 21	Polymyxin B	Loading dose on day 1 with 2.5 - 3 mg/kg. Aerosolized: ~2.5 mg/kg/day (~1.75 MIU) Mean duration: 19 d	Pneumonia 25 episodes Lower respiratory tract infection 4 episodes	16 <i>A. baumannii</i> (55%) 12 <i>P. aeruginosa</i> (41%) 1 <i>Alcaligenes xylosoxidans</i> (3%)	12/25 pts (48%)	22/29 courses (76%)	Nephrotoxicity was defined as the doubling of serum creatinine during therapy	3/29 courses (10%)

*:Duration and dosage of colistin are presented as mean $\pm$ SD and as median values where mean values were not available.

pts = patients, pt = patient, y= years, RRT = renal replacement therapy, cr = creatinine, RF = renal failure, MIU = million international units, CMS= colistimethate sodium, NA= not available, UTI= urinary tract infection

unit. Thus, definite statements regarding the effectiveness of intravenous polymyxins as monotherapy cannot be made.³¹⁻³³ In a comparative observational study of intravenous colistimethate sodium versus intravenous meropenem for the treatment of intensive care unit patients with *Acinetobacter baumannii* ventilator-associated pneumonia, the observed outcomes, including in-hospital mortality, ventilator-associated pneumonia-related mortality and clinical cure, were comparable.³⁴

Inhaled Polymyxins in Critically Ill Patients

There is no extensive experience with the use of aerosolized polymyxins for the treatment of critically ill patients with respiratory tract infections caused by multidrug-resistant Gram-negative bacteria. On the contrary, their value in preventing and treating infections due to *Pseudomonas aeruginosa* in patients with cystic fibrosis has been thoroughly established.³⁵⁻³⁷ It is worth noting that the necessity to improve the outcome among patients with pneumonia due to multidrug-resistant bacteria has led to the use of alternative methods for administration of polymyxins. Most of the experience using aerosolized polymyxins is with colistin and is likely due to the fact that polymyxin B can lead more frequently than colistimethate sodium to release of histamine during nebulization and thus, bronchoconstriction.^{38,39}

Table 2 (page 144) presents the limited evidence that exists in the recent literature with respect to the use of colistimethate sodium by nebulization in patients in the critical care setting. Aerosolized colistimethate sodium has been used as supplementary therapy to conventional intravenous antibiotic treatment for nosocomial pneumonia caused by multidrug-resistant Gram-negative microorganisms and was thought to be associated with improved outcome, suggesting that this approach merits further evaluation.^{40,41} Recently, 2 to 4 million IU per day of nebulized colistimethate sodium were administered to 21 patients with polymyxin-only susceptible *Acinetobacter baumannii* and *Pseudomonas aeruginosa* pneumonia leading to 85.7% successful clinical response. None of the patients in this study received intravenous colistimethate sodium concomitantly with aerosolized colistimethate sodium. They received other antibiotics that were, however, inactive against the isolated pathogen *in vitro*.⁴²

Toxicity

The nephrotoxicity of polymyxins has been the major vexation limiting their clinical use. However, recent data, mainly from cases series, suggest that the use of polymyxins is relatively safe provided that recommended dosages are used, renal function is closely monitored and other potential nephrotoxic agents are avoided. The D-amino acid and fatty acid molecules of the structure of polymyxins have been associated with the development of nephrotoxicity, and the suggested mechanism resembles their mechanism of action.⁴³⁻⁴⁵

In an experimental model, colistin was bound to the apical membrane of the urothelium only when the membrane potential was cell interior negative and increased the transepithelial conductance of the urinary bladder epithelium. In addition, the magnitude of the increase in conductance was dependent on the concentration of colistin and on the voltage of the membrane. The presence of calcium and magnesium decreased the colistin-induced conductance. Moreover, long-term exposure of the membrane at high concentrations of colistin resulted in incomplete return of the transepithelial conductance to normal values after the removal of colistin, suggesting that prolonged exposure to high concentrations of colistin may be associated with toxic renal effects.⁴⁶

Additionally, the use of polymyxins has been associated with the experience of several neurotoxic events, including dizziness, muscle weakness, facial and peripheral paresthesia, vertigo, confusion, ataxia and neuromuscular blockade, which can lead to respiratory failure or apnea. However, recent studies in critically ill patients are not consistent with the frequency of polymyxin-related neurotoxic events reported in the earlier literature.^{2,34} Treatment with aerosolized colistin may also be complicated with bronchoconstriction and chest tightness.³⁶ However, treatment with aerosolized β_2 -agonists before the initiation of aerosolized colistin could prevent the development of bronchoconstriction.

Conclusion

In conclusion, intravenous and aerosolized polymyxins should be considered for the treatment of critically ill patients with multidrug-resistant Gram-negative bacterial infections. Further research focusing on the appropriate dosage, clinical indications and safety profile of polymyxins is urgently needed. Meanwhile, strict use of polymyxins by clinicians worldwide is required to prevent the rapid development and dissemination of pandrug-resistant Gram-negative bacteria.¹

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Table 2. Characteristics and treatment outcomes of recently reported studies of critically ill patients who received aerosolized polymyxins for infections due to multidrug-resistant Gram-negative bacteria.

Ref #	Setting	Number of patients	Demographics/ APACHE II score	Medication used	Duration/dosage of colistin	Sites of infection	Pathogen	Mortality rates	Clinical cure	Definition of nephrotoxicity	Nephrotoxicity
41	ICU	8 pts	Mean age: 59.6 y Mean APACHE II 14.6	CMS	Dosage (range): 1.5 - 6 MIU/day Mean duration: 10.5 d	Pneumonia	7 <i>A. baumannii</i> 1 <i>P. aeruginosa</i>	1/8 pts (12.5%)	7/8 pts (87.5%)	NA	Worsening of renal function: 1 pt
42	ICU, Medical wards	21 pts	Mean age $\pm$ SD: 60.6 $\pm$ 15 y Mean APACHE II $\pm$ SD: 23.1 $\pm$ 9.1	CMS	19 pts received 2 MIU/day, 1 pt 3 MIU/day, and another pt 4 MIU/day Median duration: 14 d	Pneumonia	17 <i>A. baumannii</i> 4 <i>P. aeruginosa</i>	10/21 pts (46.7%)	18/21 pts (85.7%) of 50%, compared with the rate at the start of therapy, or a decline in renal function that necessitated renal replacement therapy	Renal failure was defined as a decrease in the estimated creatinine clearance rate	No episodes of acute renal failure
52	ICU (84%), Medical (11%), Surgical (5%)	80 pts/ 85 courses [71 aerosol, 12 courses IV or IM, 2 courses intrathecal]	Mean age $\pm$ SD: 57 $\pm$ 15 y	CMS (aerosol, IV, IM, intrathecal)	Mean duration $\pm$ SD of aerosol: 12 $\pm$ 8 d Mean duration $\pm$ SD of IV or IM: 11 $\pm$ 6 d Duration of intrathecal: 8d and 10d	Pneumonia 60 courses UTI 2 courses Bacteremia 2 courses Central nervous system infection 2 courses	69 <i>A. baumannii</i> (86%) 11 <i>P. aeruginosa</i> (14%)	14/80 pts (18%)	92% (microbiological cure)	Nephrotoxicity was defined as a serum creatinine increase of 50% or 1 mg/dl with respect to the baseline level during treatment	12 courses of iv or im were recorded. Mean $\pm$ SD baseline serum creatinine = 1.25 $\pm$ 0.79 mg/dl. Mean $\pm$ SD final serum creatinine = 1.20 $\pm$ 0.64 mg/dl. Mean $\pm$ SD baseline BUN = 8.95 $\pm$ 8.96 μ mol/l. Mean $\pm$ SD final BUN = 8.39 $\pm$ 8.06 μ mol/l.
40	Medical wards	3 pts	67 y, 45 y, 59 y	CMS	Duration: 13 d, 14 d, 11 d Dosage: 2 MIU/day, 1.5 MIU/day, 2 MIU/day	Pneumonia 2/3 pts Tracheobronchitis 1/3 pts	<i>P. aeruginosa</i>	0/3 pts	3/3 pts	NA	No episodes of acute renal failure

pts = patients, pt = patient, y= years, CMS= colistimethate sodium, MIU= million international units, NA= not available, UTI= urinary tract infection

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