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 \textit{Acinetobacter baumannii} and \textit{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 $\beta$-lactamases and metallo-$\beta$-lactamases, represent major health threats that affect patient outcomes, particularly in the intensive care unit. Strains of \textit{Acinetobacter baumannii}, \textit{Pseudomonas aeruginosa} and \textit{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.\textsuperscript{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.\textsuperscript{4-6}

**History, Mechanism of Action and Spectrum of Activity**

Polymyxins are a group of polypeptide cationic antibiotics.\textsuperscript{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 \textit{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.\textsuperscript{8-12} Specifically, several studies that assessed the safety of parenteral polymyxins reported frequent development of renal and neurological adverse effects.\textsuperscript{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.\textsuperscript{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-octanic acid or 6-methyl-epitanoic acid. The main difference between the molecules of polymyxin B and colistin is in the amino acid components.\textsuperscript{7} Colistin consists of D-leucine, L-threonine and L-\textgamma-\textalpha-diaminobutyric acid, while polymyxin B contains D-phenylalanine instead of D-leucine.\textsuperscript{7} The cationic molecules of polymyxin B and colistin compete and displace Ca\textsuperscript{2+} and Mg\textsuperscript{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.\textsuperscript{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.\textsuperscript{20} In patients with sepsis, continuous hemodialysis therapy with polymyxin-B immobilized fiber has been correlated with improvement of the survival rates.\textsuperscript{21} Their spectrum of activity includes Gram-negative aerobic bacilli only, including \textit{Acinetobacter baumannii}, \textit{Pseudomonas aeruginosa}, \textit{Klebsiella} species, \textit{Enterobacter} species, \textit{Salmonella} species, \textit{Shigella} species and \textit{Escherichia coli}. \textit{Stenotrophomonas maltophilia} strains are usually susceptible to polymyxins.\textsuperscript{22,23} On the other hand \textit{Proteus} species, \textit{Seratia} species, \textit{Burkholderia} species, \textit{Providencia} species and \textit{Edwardsiella} spp. are resistant to polymyxins.\textsuperscript{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 United Kingdom is 4–6 mg/kg 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 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 Monarch Pharmaceuticals Inc. (Bristol, TN) contains 150 mg colistin base.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{28} Both polymyxins have rapid concentration dependent bactericidal activity against Gram-negative pathogens\textsuperscript{29} and exhibit considerable post-antibiotic effects at high concentrations.\textsuperscript{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.

<table>
<thead>
<tr>
<th>Ref #</th>
<th>Setting</th>
<th>Number of patients</th>
<th>Demographics/ APACHE II score</th>
<th>Medication used</th>
<th>Duration/dosage of colistin*</th>
<th>Sites of infection</th>
<th>Pathogen</th>
<th>Mortality rates</th>
<th>Clinical cure by infection type</th>
<th>Definition of nephrotoxicity†</th>
</tr>
</thead>
<tbody>
<tr>
<td>47</td>
<td>Abdominal organ transplantation ICU</td>
<td>23 pts</td>
<td>Age (median): 52 y</td>
<td>CMS</td>
<td>Median duration (range): 17 d (7-36d)</td>
<td>Pneumonia 18 cases</td>
<td>P. aeruginosa</td>
<td>In-hospital mortality 14 pts (61%)</td>
<td>Pneumonia 10/15 pts intra-abdominal 5/8 pts Wound 1/3 pts</td>
<td>RF was defined by a requirement either for intermittent hemodialysis or for continuous venous hemofiltration</td>
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<tr>
<td>48</td>
<td>ICU</td>
<td>24 pts with sepsis/ 26 episodes of infection</td>
<td>Mean age: 44.3 y</td>
<td>CMS</td>
<td>Median duration (range): 13.5 d (4-24 d)</td>
<td>VAP 15 cases (58%)</td>
<td>P. aeruginosa</td>
<td>30-day mortality 42%</td>
<td>VAP 11/15 cases</td>
<td>RF was defined as an increase in serum creatinine &gt; 1mg/dl during treatment</td>
</tr>
<tr>
<td>49</td>
<td>ICU (52%) -transplant unit (13%) -surgical and medical wards (35%)</td>
<td>59 pts/60 nosocomial infections</td>
<td>Mean age ± SD: 42.1± 21.4 y</td>
<td>CMS</td>
<td>Mean daily dose ± SD: 152.8±62.8 mg</td>
<td>Pneumonia 20 pts (33%)</td>
<td>A. baumannii</td>
<td>22 pts (37%)</td>
<td>Pneumonia 5/20 cases UTI 10/12 cases</td>
<td>NA (information about creatinine values are provided)</td>
</tr>
<tr>
<td>34</td>
<td>ICU</td>
<td>21 pts colistin group (CO)</td>
<td>Mean age ± SD: 56.9 ± 13.1 y</td>
<td>CMS</td>
<td>Mean duration ± SD: 14.7 ± 4.1 d</td>
<td>VAP 21 A. baumannii susceptible to colistin – CO group IM group 11.2 ± 4.2 d</td>
<td>CO group: 12/21 pts</td>
<td>In-hospital mortality: 1/32 pts CO group 19.6 ± 7.2 IM group 20.5 ± 7</td>
<td>CO group: 5/21 pts IM group: 6/14 pts</td>
<td>In patients with normal renal function (cr. &lt; 1.2) – RF was defined as cr. value &gt; 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</td>
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</tbody>
</table>

*MIU q8h Post-traumatic baumannii meningitis 1 case (4%) Sinusitis 1 case (4%) UTI 1 case (4%) Sepsis of unknown primary origin 4 cases (19%) |

† RF was defined by a requirement either for intermittent hemodialysis or for continuous venous hemofiltration.
### Table 1. Continued

<table>
<thead>
<tr>
<th>Ref #</th>
<th>Setting</th>
<th>Number of patients</th>
<th>Demographic/ APACHE II score</th>
<th>Medication used</th>
<th>Duration/dosage of colistin</th>
<th>Sites of infection</th>
<th>Pathogen</th>
<th>Mortality rates</th>
<th>Clinical cure by infection type</th>
<th>Definition of nephrotoxicity</th>
<th>Nephrotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>31</td>
<td>ICU (80%) - medical, surgical wards (20%)</td>
<td>50 pts</td>
<td>Mean age ± SD: 59.2 ± 17.7 y</td>
<td>CMS</td>
<td>Mean daily dose ± SD: 4.5 ± 2.3 MIU</td>
<td>Pneumonia 18 episodes (33%)</td>
<td>A. baumannii</td>
<td>In-hospital mortality 12/50 pts (24%)</td>
<td>Pneumonia 10/18 episodes</td>
<td>RF was defined as an increase more than 50% of the baseline creatinine level to a value higher than 1.3 mg/dl or a decline in renal function requiring renal replacement therapy</td>
<td>450 pts (8%)</td>
</tr>
<tr>
<td>2</td>
<td>ICU</td>
<td>43 pts</td>
<td>Mean age ± SD: 56.5 ± 16.2 y</td>
<td>CMS</td>
<td>Dosage: 3 MIU q8h</td>
<td>Pneumonia (VAP) 21 pts</td>
<td>P. aeruginosa</td>
<td>In-hospital mortality 12/43 pts (28%)</td>
<td>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 at the initiation of colistin treatment.</td>
<td>843 pts (18.6%)</td>
<td></td>
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<tr>
<td>3</td>
<td>ICU</td>
<td>55 pts colistin group (CO) 130 pts Non-colistin group (Non-CO)</td>
<td>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</td>
<td>CMS</td>
<td></td>
<td>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</td>
<td>CO group: 19 A. baumannii 36 P. aeruginosa 69 A. baumannii</td>
<td></td>
<td>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</td>
<td>NA</td>
<td></td>
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</tbody>
</table>
Table 1. Continued

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<th>Mortality rates</th>
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<th>Definition of nephrotoxicity†</th>
<th>Nephrotoxicity‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>ICU</td>
<td>14 pts</td>
<td>Mean age: 49 y</td>
<td>CMS</td>
<td>Dosage: 2 MIU q8h</td>
<td>VAP 10 pts</td>
<td>A. baumannii</td>
<td>7/14 pts (50%)</td>
<td>9/14 pts (64%)</td>
<td>NA</td>
<td>1 pt had deterioration of renal function (creatinine up to 2.8 mg/dl).</td>
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<td></td>
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<td></td>
<td>Mean duration: 12 d VAP and bacteremia 2 pts VAP and surgical site infection 2 pts</td>
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<tr>
<td>51</td>
<td>Mainly ICU</td>
<td>17 pts/19 courses</td>
<td>Median age: 51 y</td>
<td>CMS</td>
<td>Mean ± SD daily dose: 4.4 MIU (352 mg) ± 2.1 MIU (168 mg) Mean ± SD duration: 43.4 ± 14.6 d</td>
<td>Pneumonia 13/19 courses Bacteremia 1/19 courses UTI 2/19 courses Meningitis 2/19 courses Surgical site infection 1/19 courses</td>
<td>A. baumannii</td>
<td>7/17 pts (41%)</td>
<td>14/19 courses (74%)</td>
<td>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</td>
<td>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.</td>
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<td>Median APACHE II: 14</td>
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<td>52</td>
<td>ICU (92%)</td>
<td>25 pts/29 courses</td>
<td>Mean age: 55 y</td>
<td>Polymyxin B</td>
<td>Loading dose on day 1 with 2.5 - 3 mg/kg Aerosolized: -2.5 mg/kg/day (1.75 MIU) Mean duration: 19 d</td>
<td>Pneumonia 25 episodes Lower respiratory tract infection 4 episodes</td>
<td>A. baumannii</td>
<td>16/25 pts (65%)</td>
<td>23/29 courses (76%)</td>
<td>Nephrotoxicity was defined as the doubling of serum creatinine during therapy</td>
<td>3/29 courses (10%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[21 courses 4 x 6 courses aerosol, 2 courses # combination]</td>
<td></td>
<td></td>
<td></td>
<td>16 A. baumannii</td>
<td>16/25 pts (65%)</td>
<td>22/29 courses (76%)</td>
<td>Nephrotoxicity was defined as the doubling of serum creatinine during therapy</td>
<td>3/29 courses (10%)</td>
<td></td>
</tr>
</tbody>
</table>

*Duration and dosage of colistin are presented as mean ± 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
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.50,41 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 β2-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

**References**

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.

<table>
<thead>
<tr>
<th>Ref #</th>
<th>Setting</th>
<th>Number of patients</th>
<th>Demographics/ APACHE II score</th>
<th>Medication used</th>
<th>Duration/dosage of colistin</th>
<th>Sites of infection</th>
<th>Pathogen</th>
<th>Mortality rates</th>
<th>Clinical cure</th>
<th>Definition of nephrotoxicity</th>
<th>Nephrotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>41</td>
<td>ICU</td>
<td>8 pts</td>
<td>Mean age: 59.6 y</td>
<td>CMS</td>
<td>Dosage (range): 1.5 - 6 MIU/day</td>
<td>Pneumonia</td>
<td>7 A. baumannii</td>
<td>1/8 pts (12.5%)</td>
<td>7/8 pts (87.5%)</td>
<td>NA</td>
<td>Worsening of renal function: 1 pt</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Mean APACHE II: 14.6</td>
<td></td>
<td>Median duration: 10.5 d</td>
<td></td>
<td>1 P. aeruginosa</td>
<td></td>
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<tr>
<td>42</td>
<td>ICU, Medical wards</td>
<td>21 pts</td>
<td>Mean age ± SD: 60.6 ± 15 y</td>
<td>CMS</td>
<td>19 pts received 2 MIU/day, 1 pt 3 MIU/day, and another pt 4 MIU/day</td>
<td>Pneumonia</td>
<td>17 A. baumannii</td>
<td>10/21 pts (46.7%)</td>
<td>18/21 pts (85.7%)</td>
<td>Renal failure was defined as a decrease in the estimated creatinine clearance rate of 50%, compared with the rate at the start of therapy, or a decline in renal function that necessitated renal replacement therapy</td>
<td>No episodes of acute renal failure</td>
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<td>Mean APACHE II: 23.1 ± 9.1</td>
<td></td>
<td>Median duration: 14 d</td>
<td></td>
<td>4 P. aeruginosa</td>
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<tr>
<td>52</td>
<td>ICU (84%), Medical (11%), Surgical (5%)</td>
<td>80 pts/ 85 courses (71 courses aerosol, 12 courses IV or IM, 2 courses intrathecal)</td>
<td>Mean age ± SD: 57 ± 15 y</td>
<td>CMS (aerosol, IV, IM, intrathecal)</td>
<td>Mean duration ± SD of aerosol: 12 ± 8 d</td>
<td>Pneumonia 60 courses UTI 2 courses</td>
<td>69 A. baumannii (88%)</td>
<td>14/80 pts (18%)</td>
<td>92% (microbiological cure)</td>
<td>Nephrotoxicity was defined as a serum creatinine increase of 50% or 1 mg/dl with respect to the baseline level during treatment</td>
<td>12 courses of iv or im were recorded. Mean ± SD baseline serum creatinine = 1.25 ± 0.79 mg/dl. Mean ± SD final serum creatinine = 1.20 ± 0.64 mg/dl. Mean ± SD baseline BUN = 8.95 ± 8.96 µmol/l. Mean ± SD final BUN = 8.39 ± 8.06 µmol/l.</td>
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<td></td>
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<td></td>
<td>Mean duration ± SD of IV or IM: 11 ± 6 d</td>
<td>Bacteraemia 2 courses</td>
<td>11 P. aeruginosa (14%)</td>
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<td></td>
<td></td>
<td>Duration of intrathecal: 8d and 10d</td>
<td>Central nervous system infection 2 courses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>Medical wards</td>
<td>3 pts</td>
<td>67 y, 45 y, 59 y</td>
<td>CMS</td>
<td>Duration: 13 d, 14 d, 11 d</td>
<td>Pneumonia 2/3 pts Tracheobronchitis 1/3 pts</td>
<td>P. aeruginosa</td>
<td>0/3 pts</td>
<td>3/3 pts</td>
<td>NA</td>
<td>No episodes of acute renal failure</td>
</tr>
</tbody>
</table>

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


51. Falagas ME, Rizos M, Bliziotis IA, Rellos K, Kasiakou SK, Michalopoulos A. Toxicity after prolonged (more than four weeks) administration of intravenous colistin. BMC Infect Dis 2005;5:1.

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