Review Article

POLYMYXINS – A REVIEW FOCUSING ON THEIR NEPHROTOXICITY

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ABSTRACT

Polymyxins are polypeptide antibiotics with strong action against Gram-negative bacteria. Their use was almost halted between 1970 and 1980 with the advent of less toxic compounds. The emergence of multi-resistant Gram-negative bacterial strains, mainly in intensive care unit patients, and the absence of new antimicrobials that were effective against these pathogens, there has been renewed interest in polymyxins in recent years. The major adverse effect of this class of antibiotics is nephrotoxicity. Currently, only polymyxins B and E are used in clinical practice. Polymyxin E, which is widely employed and investigated, is known as colistin, and is used in the form of colistimethate sodium to reduce nephrotoxicity. There are no consistent data about the prevalence of renal injury associated with the use of polymyxins or about the risk factors these antibiotics pose in terms of nephrotoxicity. The aim of this study is to review the main aspects of polymyxin pharmacodynamics, to provide a better understanding of their mechanisms of renal injury, and to compare the different prevalence rates of renal injury associated with the use of these antibiotics.

KEY WORDS: Polymyxin B. Colistin. Acute renal failure. Nephrotoxicity.

Polymyxins belong to a group of active antibiotics against several Gram-negative bacteria. Synthesized by *Bacillus polimyxa* strains, they were independently described in 1947 by U.S. and English researchers and the generic name of polymyxins was adopted for the antibiotics derived from this microorganism.[1] They contain five closely related substances, called polymyxins A, B, C, D and E, the latter of which is known as colistin, produced by *Bacillus colistinus*. Only polymyxins B and E have clinical use, due to the high toxicity of the other polymyxins.[2]

Antimicrobial activity

The antimicrobial spectrum includes only Gram-negative organisms. An epidemiological surveillance program (SENTRY - 2001 to 2004) found that polymyxin B was excellent against Pseudomonas aeruginosa (1.3% of resistance) and Acinetobacter spp (2.1% of resistan ce), with an $MIC_{50} \leq 1$ mg/L and $MIC_{90} \leq 2$mg/L for both pathogens, and against Citrobacter spp., Escherichia coli and Klebsiella spp (MIC_{90}, ≤ 1 mg/L; less than 2% of resistance). Sensitivity to Enterobacter spp (83.3% of susceptibility; MIC_{50}, ≤ 1 mg/L) and Stenotrophomonas maltophilia (72.4% of susceptibility; $MIC_{50} \leq 1$ mg/L) varied more sharply. Sensitivity is poorer ($MIC_{50} >$ 8 mg/L) to Burkholderia cepacia (11.8% of susceptibility), Serratia spp. (5.4% of susceptibility), indole-positive Proteus spp. (1.3% of susceptibility) and Proteus mirabilis (0.7% of susceptibility).[3]

Polymyxins are not active against Gram-positive bacteria and fungi. The bactericidal activity of this class of antibiotics has remained virtually unchanged since its introduction,[4, 5] notwithstanding the fact that some resistance has already been observed, and that the combined use of antibiotics in order to potentiate their bactericidal effect has also been reported.[6, 7]

Chemical structure of polymyxins

Polymyxins are cyclic polycationic decapeptides that contain a heptapeptide ring and have a high rate of 2,4-diaminobutyric (Dab) acid and a fatty acid bound to the peptide by an amide bond. The ring is formed by the α-amine and carboxyl groups of the Dab residue in position 4, with an additional peptide chain attached through the g-amino group of this residue. Colistin (polymyxin E) differs from polymyxin B because it has D-leucine in lieu of D-phenylalanine in position 6. Colistimethate sodium (CMS) is a colistin derivative obtained from the reaction with formaldehyde and sodium bisulfite. This derivative is less potent comparatively to the original compound and apparently causes fewer adverse effects.[2,4,8] After administration, CMS is converted into "in vivo" colistin and both forms circulate within the body. A recent study suggested that CMS is inactive and that its bactericidal effect depends on "in vivo" metabolization in order to form colistin, which would be the only active compound.[9]

Mechanism of action

Polymyxins are amphipathic antibiotics and act primarily upon the external and cytoplasmic membranes, with similar action to that of simple cationic detergents. They bind to cell envelope components such as phospholipids and liposaccharides (LPS), displacing, in a competitive fashion, the Ca and Mg ions that act as membrane stabilizers, leading to membrane

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rupture and to the loss of cellular contents, thus killing the bacterium. This action seems to be inhibited in the presence of these bivalent cations.[4] The binding and inactivation capacity of the liposaccharide (LPS), molecule that is related to the development of sepsis and septic shock, has prompted research into its capacity in treating these syndromes, inhibiting or reducing the inflammatory stimulus induced by LPS.[10] In this regard, devices for LPS removal and inflammatory mediators, such as dialysis filters impregnated with polymyxin B, have been used and achieved some success.[11, 12]

Commercially available preparations

Polymyxin E (colistin) is commercially available as sulfate, used as a topical agent for intestinal decontamination, and as CMS for parenteral use (intravenous, intramuscular, intrathecal and aerosolized). Polymyxin B sulfate is used as a topical medication (skin, ears and eyes) and parenterally (intravenous and intrathecal administration).[13]

Pharmacokinetics/Pharmacodynamics

Older information about the pharmacokinetics of these antibiotics proves unreliable with regard to CMS, as the methods used did not distinguish CMS from colistin, its active form. Therefore, these studies must be viewed with caution. A recent study, using high-performance liquid chromatography, assessed 14 patients with normal renal function but with severe infections caused by multiresistant Gram-negative bacilli, treated with 225 mg of IV CMS every 8 hours (one patient received 150 mg every 8 hours) for at least 2 days, and found maximum and minimum concentrations of 2.93 mg/L (standard deviation - SD = 1.24) and 1.03 mg/L (SD = 0.44), respectively. The clearance, distribution volume and half-life with their respective SD were 13.6 (5.8) L/h, 139.9 (60.3) L and 7.4 (1.7) hours, respectively. It should be remarked that these doses were associated with a suboptimal C_{MAX}/MIC ratio for many strains of Gram-negative bacilli (MIC £ 2 mg/mL).[14] Studies that assessed polymyxin B sulfate are more reliable. A recent study determined the serum concentration of polymyxin B1 (the largest constituent of polymyxin B sulfate) in nine patients after intravenous use. The half-life was 13 hours. Also, high protein binding (> 95%) and a distribution volume of approximately 1.39 L/kg[15] were observed.

The bactericidal effect of these antibiotics had a quick onset of action and depended on the concentration used. In a study about polymyxin B, the daily dose (but not the frequency of doses) played an important role in determining antibiotic action, and the AUC/MIC (area under the curve/minimum inhibitory concentration) ratio seems to be the pharmacodynamic parameter most widely associated with the bactericidal effect.[16]

Dosing

Polymyxin B is used at the dose of 1.5 to 2.5 mg/kg/day (1.0 mg of polymyxin B sulfate = 10,000 IU) in patients with normal renal function (creatinine clearance > 80 mL/min).[17] In patients with abnormal renal function, it is recommended that a dose of 2.5 mg/kg be given on the first day, adjusting the subsequent doses according to creatinine clearance (CrCl). Between 30 and 80 mL/min, 1.0 to 1.5 mg/kg/d should be administered; with CrCl < 30 mL/min, the dose ranges from 1.0 to 1.5 mg/kg every 2 or 3 days; and in anuric patients, administration of 1.0 mg/kg must be made every 5 to 7 days.[18] CMS sold in the USA (colymycin M@) is used at the dose of 5.0 mg/kg/day in patients with normal creatinine levels (Cr < 1.2 mg/dL), given in three divided doses. When Cr ranges from 1.3 and 1.5 mg/dL, a dose of 2.5 to 3.8 mg/kg/d is used. For Cr between 2.6 and 2.5 mg/dL, the recommended dose is 2.5 mg/kg/d whereas for Cr between 2.6 and 4.0 mg/dL it is 1.5 mg/kg/d.[19]

The removal capacity of these substances by dialysis has yielded conflicting results. Li et al.[20] retrieved colistin and its CMS derivative from plasma and dialysis fluid during continuous venovenous hemodiafiltration using high-performance liquid chromatography, suggesting that dose adjustment is smaller in patients submitted to this procedure. Sarria et al.[21] failed to detect polymyxin B in the dialysate during continuous venovenous hemodialysis although its presence in the plasma had been confirmed by repeated tests, suggesting that the drug is not dialysable and therefore supplemental doses would not be necessary in patients submitted to dialysis.

Toxicity

Polymyxins have no longer been used on a routine basis given the development of less toxic antimicrobials. In the 1990s, with the emergence of multiresistant bacteria, including those resistant to β-lactams, aminoglycosides and quinolones, which caused nosocomial infections, especially in intensive care units,[2, 22, 23, 24] the interest in polymyxins was renewed, and consequently several reviews have dealt with them.[25, 26]

The most remarkable adverse effects of these drugs are nephrotoxicity (chiefly acute renal failure) and neurotoxicity. Other effects include allergies that cause skin injury (urticaria-like), pain on injection site (intramuscular injection), thrombophlebitis (IV injection), fever and eosinophilia.[17, 19] Information about their use in humans during pregnancy is limited. Kazy et al.[27] did not find evidence of human teratogenicity caused by the use of polymyxin B.

Neurotoxicity

Polymyxin-induced neurotoxicity is characterized by weakness, peripheral and facial paresthesias, ophthalmoplegia, swallowing difficulty, ataxia, eyelid ptosis and even muscle block with respiratory failure and necessity for ventilatory support. The symptoms resolve after the drug is discontinued. Most patients with neurotoxicity had concomitant renal failure.[28,29] Neurological disorders were described in 7.3% of 317 courses of treatment with intramuscular CMS.[30]

Nephrotoxicity

The development of renal injury, especially acute renal failure (ARF), is the major limiting factor for the use of this class of antibiotics. There is an increase in the levels of serum urea and creatinine and a decrease in CrCl, in addition to hematuria, proteinuria, cylindruria and oliguria. The mechanism of renal injury seems to be related to the contents of d-aminobutyric acid and fatty acid of the molecule, and resembles the effect of the antibiotic on the outer bacterial membrane. Membrane permeability increases, making the flow of cations, anions and water easier and causing edema and cell lysis. This action is

seemingly dependent upon the concentration and length of exposure to the antibiotic.[26] In a large study about IM CMS, six patients were clinically diagnosed with drug-related acute tubular necrosis, with histological confirmation in three of them.[30] Acute interstitial nephritis due to hypersensitivity to the antibiotic has also been reported.[31, 32]

Experimental studies

Moyer et al. assessed the IV administration of polymyxin B in dogs at the dose of 2.5 mg/kg and observed a reduction in glomerular filtration and in plasma renal flow. The same dose given IM did not cause significant renal problems. The histological examination of the animals which presented with abnormal renal findings revealed diffuse edema in renal tubules.[1] In comparative studies about colistin, CMS and polymyxin B methanesulfonate, polymyxin B sulfate proved more active, but more toxic, especially at higher doses, causing renal function to decrease markedly.[8,33]

Studies in humans

Yow EM et al. assessed the administration of polymyxin B (2.5 mg/kg) in 10 healthy subjects and found renal dysfunction in three out of four individuals with CrCl < 85 mL/min. They also assessed 26 patients treated for *P. aeruginosa* infection, but they did not encounter significant renal problems.[34] Another previous study correlated high CMS doses with an increase in urea and creatinine levels and a decrease in CrCl, with recovery of the renal function after drug discontinuation.[35]

In 288 patients (317 treatments with IM CMS), Koch-Weser et al. detected nephrotoxicity in 20.2%, with a higher incidence among those patients with previously impaired renal function and among older ones. Mortality did not differ between patients with and without ARF.[30]

Studies of patients with cystic fibrosis treated with CMS indicated mild renal impairment. In the larger study, including 52 patients (135 treatments), none of the subjects developed nephrotoxicity;[36] in another study comprising 12 patients, there was a reversible increase in urea or creatinine levels in three individuals,[37] whereas Reed et al.[38] observed an increase in serum creatinine only in one out of 31 patients (proteinuria in 14 patients). The small number of patients who developed renal injuries can be explained by the type of patients assessed, usually younger and less severely ill, unlike individuals without cystic fibrosis who are treated with this class of antibiotics. Quite often, they have acute and severe disease, requiring ICU admission, with comorbidities and with several other risk factors for nephrotoxicity.

Levin et al.[39] investigated 59 patients who received CMS and found 37% of ARF. This complication was more frequent among patients with previous renal impairment (58%) than among those with normal renal function (27%).

Falagas et al.[40] assessed patients on prolonged use of CMS, for over 4 weeks (mean of 43.4 ± 14.6 days). Only one patient showed reversible increase in creatinine levels during treatment, and this patient had previously impaired renal function. In another study, the same author assessed 21 patients who received CMS for at least 7 days. ARF occurred in three patients (two eventually died). There was some correlation between the accumulated CMS dose and the progressive increase in serum

Table 1 – Recent studies on colistimethate sodium nephrotoxicity

Author/year of publication	Patients (type, number, mean age)	Dosing	Definition of Nephrotoxicity	Nephrotoxicity (ARF)	Mortality / Therapeutic response
Levin et al. (1999)39	ICU Transplant (65%) 59 patients 42.1 ± 21.4 years	2.5 – 5.0 mg/kg/d (adjust if Cr > 1.2 mg/dL)	Increase in CrB	ARF: 37% CrB £ 1.5 mg/dL - ARF = 27% CrB > 1.5 mg/dL - ARF = 58%	37%
Garnacho-Monteiro et al (2003)52	ICU 21 patients 56.9 ± 13.1 years	2.5 – 5.0 mg/kg/d (adjust if Cr > 1.2 mg/dL)	CrB < 1.2: > 2 mg/dL, or decrease in CrCl > 50% or need for dialysis. CrB ≥ 1.2: > 50% of CrB, or decrease in CrCl > 50% or need for dialysis	ARF: 24% .	61.9%
Michalopoulos AS et al. (2005)45	ICU 43 patients 56.5 ± 16.2 years	3 MU 3x/d, adjust if CrB ≥ 1.3 mg/dL ≥ 48 hrs of treatment	CrB ≤ 1.2: increase ≥ 2 mg/dL. CrB > 2 mg/dL: twofold increase in CrB	ARF: 18.6% Patients with CrB > 2 mg/dL: 62.5% Patients with CrB ≤ 1.2 mg/dL: 8.5%	In-hospital mortality: 27.9% ARF mortality: 100%
Falagas ME et al. (2005)42	ICU 17 patients (19 treatments) 51 years	5 mg/kg/d ≥ 4 weeks of treatment	ARF: increase > 50% of CrB, greater than 1.3 mg/dL, or need for dialysis	1% of ARF at the end of treatment	In-hospital mortality: 41.2%

Falagas ME et al. (2005)43	ICU - 81% 21 patients 67 ± 16 years	Average dose: 5.5 ± 1.9 MIU. ≥ 7 days of treatment.	ARF: increase > 50% of CrB, greater than 1.3 mg/dL, or need for dialysis	ARF: 14.3%	In-hospital mortality: 47.6%.
Kasiakou et al. (2005)44	ICU - 80% 50 patients. (54 treatments) 59.2 ± 17.7 years	2 MU every 8 hrs ≥3 days of treatment	ARF: increase > 50% of CrB, greater than 1.3 mg/dL, or need for dialysis	ARF: 8%. Patients with CrB > 1.3 mg/dL: 18% Patients with CrB ≤ 1.3: 5%	In-hospital mortality: 24%. ARF was not correlated with death.
Reina R et al (2005)53	ICU 55 patients 41 ± 16 years	5 mg/kg/d every 8 hrs. Adjust if CrB ≥ 1.3 mg/dL	ARF: increase in CrB ≥ 2.0 mg/dL, or decrease in CrCl > 50% or need for dialysis.	ARF: 0%	In-hospital mortality: 29%
Hachem RY et al. (2006)55	Cancer patients (68% ICU) 31 patients Median: 52 years	5 mg/kg/d	ARF: increase in CrB ≥ 50% or increase of 1 mg/dL in CrB.	ARF: 23%.	In-hospital mortality: 26%
Kallel H et al. (2006)46	ICU 75 patients (78 treatments) 48 ± 20 years	75 - 150 x 103 U/kg/d (5.5 ± 1.1 MU/d)	ARF: if serum Cr > 150 μmol/L or BUN > 10 mmol/L (when renal function is normal)	ARF: 9% - all with normal renal function at baseline.	Favorable therapeutic response: 76.9%
Cubillos AF et al. (2007)48	Mainly ICU 22 patients (24 treatments) 58.2 (16 - 88 years)	2 to 5 mg/kg/d	Normal renal function → increase > 2 mg/dL. Previous renal disease → twofold increase in CrB	ARF: 0%.	In-hospital mortality: 54.5%
Koomanachai P et al. (2007)47	57% in the ICU 78 patients 63.5 years (18 - 103)	5 mg/kg/d	Twofold increase in CrB or 30% decrease in baseline CrCl	ARF: 30.8 %	30-day mortality: 46.2%
Kallel H et al. (2007)54	ICU 60 patients 43.4 ± 18.8 years	6 MU/d ¸ 3 times	–	ARF: 0%	ICU: 41.7% In-hospital mortality: 41.7%
Oliveira MS et al. (2008)56	Mainly ICU (93%) 82 patients 63 years (8 - 87) - Median	(Mean) CMS: 5.1 MU/d Polymyxin B: 1 MU/d	If Cr B £ 1.4: twofold increase in CrB If Cr B > 1.4: increase in Cr by 1 mg/dL	ARF: 26%	In-hospital mortality: 77%
Pintado V et al. (2008)51	Mainly ICU 60 patients 52 ± 21.5 years	2.5 to 5.0 mg/kg/d	If Cr < 1.4 mg/dL → increase in CrB > 2 mg/dL. If Cr ≥ 1.4 mg/dL → 50% increase in the baseline value or need for dialysis.	10.9% .	30-day mortality: 26.7%
Bassetti et al. (2008)50	ICU 29 patients 46 ± 14 years	2 MU every 8 hrs	If Cr < 1.2 mg/dL: ARF > 2 mg/dL or 50% decrease in CrCl. If Cr ≥ 1.2 mg/dL: increase in CrB ≥ 50% or 50% decrease in CrCl.	10%	30-day mortality: 31%

CrCl: creatinine clearance, CrB: creatinine at baseline, Cr: serumcreatinine, MU: million units

Table 2 – Recent studies on IV polymyxin B nephrotoxicity

Author/year of publication	Patients (type, number and mean age)	Dosing	Definition of nephrotoxicity	Nephrotoxicity	Mortality
Ouderkirk et al (2003)[40]	Tertiary care hospital 60 patients 61years (22-90)	1.5-2.5 mg/kg/d	Twofold increase in CrB for value ≥ 2 mg/dL	14%	20% with ARF: 57% without ARF: 15%
Sobieszczyc et al. (2004)[7]	ICU (92%) 25 patients.(29 treatments) 55 years (20 - 84)	2.5-3.0 mg/kg. ≥ 2 days of treatment	Twofold increase in CrB	6%	End of treatment: 21% In hospital: 48%
Holloway et al. (2006)[41]	ICU 33 patients 41 years	Average dose: 130 mg/d (18.6 - 300 mg/d). At least 2 doses	0.5 mg/dL increase in CrB or increase ≥ 50% in CrB or decrease in CrCl ≥ 50%	21%	27%
Furtado et al. (2007)[49]	ICU 74 patients 51/58 years	1.5-2.5 mg/kg/d (continuous IV) ≥ 2 days of treatment	Need for dialysis, serum creatinine > 2.0 mg/dL or twofold increase in CrB during treatment.	9.4% 5.7% favorable response group 12.8% unfavorable response group.	Favorable response: 47.3% In-hospital mortality: 74.3%
Pastewski AA et al. (2008)[52]	ICU 16 patients (17 treatments) 72,2 ± 13,9 years	1.5-2.5 mg/kg/d	Definition of ARF: increase CrB ≥ 0.5 mg/dL or decrease in CrCl ≥ 50%	55%	In-hospital mortality: 63%

CrCl = creatinine clearance, CrB = creatinine at baseline, Cr = serum creatinine

creatinine levels.[41] Kasiakou et al.[42] investigated 50 ICU patients (54 treatments) who had received CMS for at least 3 days. ARF was observed in four patients (8%), two of them with previously impaired renal function. Michelopoulos et al.[43] assessed 43 ICU patients (77% > 50 years) treated with CMS. Eight patients (18.6%) developed ARF. All of their patients died. Kallel et al.[44] assessed 75 ICU patients (78 treatments) treated with CMS. In 76.9% of the cases the outcome was favorable. Seven patients (9%) developed ARF.

Koomanachai et al.[45] investigated 78 CMS-treated patients with mean age of 63.5 years. Nephrotoxicity was observed in 24 patients (30.8%), 17 of whom had other predisposing factors for renal injury (other nephrotoxic drugs, chronic renal disease and hypovolemia). Renal impairment was mild and reversible without the need of dialysis. The 30-day mortality amounted to 46%.

Fica et al.[46] assessed 22 patients submitted to 24 treatments with CMS. They did not find renal dysfunction in this series, and in-hospital mortality was 54.5%.

Bassetti et al.[47] evaluated 29 patients infected by *A. baumannii* treated with CMS in combination with IV rifampicin. Three patients developed ARF, and all of them had previous renal impairment. The 30-day mortality corresponded to 31%. Pintado et al.[48] assessed 60 patients treated with CMS for over 48 hours. Nephrotoxicity was detected in 55 patients. Six patients (10.9%) developed ARF, and four of them had previous renal dysfunction. Despite the large number of patients who received CMS in combination with aminoglycosides (48.3%), the ARF rate was similar to that of patients who were not treated with this drug combination. The 30-day mortality amounted to 26.7%.

Published studies that assess the use of polymyxin B are less frequent, probably due to the arguably lower toxicity of CMS. Ouderkirket al.[49] evaluated 60 patients treated with polymyxin B and observed 14% of ARF. These patients were older (mean age of 76 *vs* 59 years, $p = 0.02$) and had a higher mortality rate (57% *vs* 15%, $p<0.02$). Nine patients had abnormal CrB, a factor that contributes towards the development of ARF; however, curiously enough, none of the patients developed ARF. The same was observed by Holloway et al.,[50] who did not find patients with abnormal renal function amidst the 27% of the patients who developed ARF, even though seven out of 33 patients developed this condition. The seven patients who developed ARF did not require dialysis, and in five of them creatinine levels were back within normal range after drug discontinuation. Mortality corresponded to 27%. Another study on polymyxin B assessed 23 patients with pulmonary infection. Only one patient developed ARF. Mortality at the end of treatment amounted to 21% and in-hospital mortality was as high as 48%.[7] Furtado et al.[51] investigated 74 patients with nosocomial pneumonia caused by *P. aeruginosa* treated with polymyxin B for at least 2 days. The nephrotoxicity rate was 9.4%. No difference was observed in terms of ARF between patients with favorable and unfavorable outcomes. In-hospital mortality was equivalent to 74.3%. In another recent study on polymyxin B, in which ICU patients with bacteremia and UTI were assessed, ARF affected 55% of the patients; however, the definition of ARF was more accurate, mortality was as high as 63%.[52]

In several recent studies comparing polymyxins with other anti-pseudomonas antibiotics, including carbapenems and ampicillin-sulbactam, among others, no difference was noted

in nephrotoxicity between the different antibiotics used and polymyxins.[53-57]

Tables 1 and 2 summarize the recent assessments of treatments with polymyxin B sulfate and CMS, showing the number and type of patients, definition and incidence of nephrotoxicity (ARF) and mortality.

In conclusion, reports on the nephrotoxicity of polymyxins have revealed rates of 15 to 55%. The ambiguous definition of ARF does not allow for more significant conclusions. Some studies show a higher prevalence in patients with previous renal impairment, in older ones and in those who receive high doses of this antibiotic, which are not adjusted according to the degree of renal impairment. It is particularly difficult to determine to what extent these drugs contribute to renal injury as most patients treated with this antibiotic have severe diseases, require ICU care and almost always have other factors that predispose to renal dysfunction. Therefore, the nephrotoxicity of these drugs is likely lower than the prevalence rates obtained. It is important to employ all available mechanisms for renal protection in patients treated with these antibiotics, such as maintenance of blood volume and caution with the administration of other potentially nephrotoxic drugs, in addition to the careful control of renal function.

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