Chapter

Understanding the Harmful Impact of Polymyxins on *Acinetobacter baumannii*

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Abstract

Nosocomial infections caused by carbapenem-resistant *Acinetobacter baumannii* (CRAB) have become a global concern. The extensive antibiotic resistance of CRAB has significantly limited treatment options, while its prevalence in hospital outbreaks has amplified infection rates. This scenario has led to a resurgence of interest in polymyxins, an older class of antibiotics previously overlooked due to perceived toxicity. Polymyxins, cationic polypeptide antibiotics, now represent a last-resort treatment option. Despite their historical use, modern assessment methods have only recently been applied to evaluate polymyxins. Two polymyxins are available for clinical use: polymyxin B and colistin (polymyxin E). Notably, the administration of these drugs is hindered by toxicities, primarily nephrotoxicity and neurotoxicity, alongside less common adverse effects such as injection pain, hypersensitivity reactions, and bronchospasms.

Keywords: *Acinetobacter baumannii*, polymyxin, toxicity, nephrotoxicity, neurotoxicity

1. Introduction

Antimicrobial resistance (AMR) has escalated into a global healthcare crisis, rendering many pathogens resistant to current treatments [1]. A comprehensive analysis estimated 1.27 million deaths attributable to bacterial AMR in 2019 [2], and projections indicate that 2050 annual AMR-related deaths could reach ten million [3].

Over the past three decades, *Acinetobacter baumannii* has emerged as a formidable healthcare challenge, particularly due to multidrug-resistant (MDR) strains, resistant even to carbapenems [4, 5]. MDR rates for *A. baumannii* surpass those of other nosocomial pathogens [6]. *A. baumannii*, a Gram-negative non-fermentative coccobacillus of the *Moraxellacecae* family, thrives in healthcare settings owing to its antibiotic resistance and desiccation tolerance [7].

Managing *A. baumannii* infections is complex due to its diverse resistance mechanisms, with carbapenem resistance (CR) being particularly concerning. The World Health Organization (WHO) classifies carbapenem-resistant *A. baumannii* (CRAB) as a critical priority, given its threat to human health [8]. During the SARS-CoV-2

pandemic, CRAB infections further complicated patient outcomes, with high resistance rates (91.2%) observed [9].

A significant subset of CRAB isolates is extensively drug-resistant (XDR; i.e., non-susceptible to ≥1 agent in all but ≤2 classes) or pan drug-resistant (PDR; i.e., non-susceptible to all antimicrobial agents have been reported worldwide) [10–12], compounding the challenge. Limited effective antibiotic options against CRAB pose a substantial health challenge. Polymyxins, though previously overshadowed, regained prominence in the late 1990s due to their activity against carbapenem-resistant (CR) infections [13]. However, new-generation antimicrobials, particularly β-lactam/β-lactamase inhibitors, have largely replaced polymyxins in CR Gram-negative bacterial infections. Conversely, polymyxins are vital for tackling resistant pathogens [13–15], especially where new agents are unavailable [16]. Nonetheless, they come with adverse effects, including allergic reactions, neurotoxicity, and nephrotoxicity [17].

2. Polymyxins

2.1 History of discovery

Polymyxins are cationic polypeptide antibiotics derived from *Bacillus polymyxa*, pivotal in treating carbapenem-resistant Gram-negative bacteria. The initial antibacterial activity was reported in 1947 [18, 19], leading to the isolation of antibiotics named polymyxin [20] and aerosporin [18, 21]. Despite the structural similarity, they were classified as belonging to the same class [22–25]. Polymyxin B and polymyxin E (colistin) differ in a single amino acid (D-Phe replaces D-Leu) [26, 27] and are the clinical variants among over 15 known polymyxins [13–15, 28, 29]. These peptides share a cyclic ring structure with hydrophilic and hydrophobic components, enabling them to disrupt cell membranes [13, 29, 30].

2.2 Structure

Polymyxins' structure resembles antimicrobial peptides deployed by eukaryotes against pathogens. They are natural non-ribosomal cyclic lipopeptides weighing around 1.2 kDa (**Figure 1**) and consist of a cyclic ring of amino acids with a tripeptide chain, which binds to the lipid part of the molecule. The decapeptide core of polymyxins contains an intramolecular loop of starch-linked heptapeptides between the amino group on the side chain of the aminobutyric acid (Dab) residue at position four and the carboxyl group on the C-terminal threonine residue. They also have several other distinctive structural features, including five non-proteogenic Dab residues positively charged at physiological pH, conserved hydrophobic residues at positions 6 and 7, and an N-terminal acyl group [31]. The cationic peptide ring of these antibiotics is the same between the two polymyxins, except for a single amino acid: a D-Leu from colistin is relocated by D-Phe to polymyxin B [14, 26, 27, 29–32]. However, the pharmacokinetics of polymyxin B and colistin differ notably due to the different pharmaceutical forms in which they are administered—active and prodrug form, respectively [33]. Its mechanisms of action occur through the rupture of the external and cytoplasmic membranes of the bacteria, causing loss of the contents of the cell's interior [34]. Polymyxin B comprises at least four components and polymyxin B1 to B4, which differ only in the portion containing fatty acids, polymyxin B1 and B2 being in greater proportion [35].

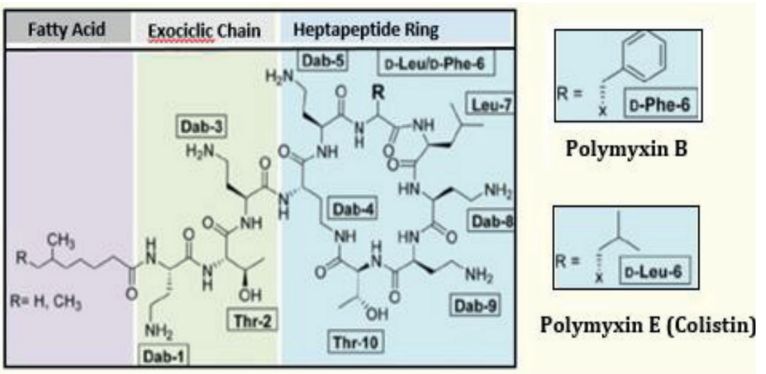

Figure 1.
Cyclic lipopeptide structure of polymyxin B (1). Colistin (polymyxin E) features a substitution of one (D-Leu) with one (D-Phe) (2).

2.3 Mechanism of action

Polymyxins exert rapid bactericidal effects by interacting with lipopolysaccharides (LPS) in the bacterial outer membrane, inducing disruptions that compromise membrane integrity. LPS, a critical component of the bacterial outer membrane, encompasses the O antigen, polysaccharide core, and lipid A. The positive charge of the polymyxin ring facilitates its binding to the outer membrane's lipid A, leading to the displacement of stabilizing Mg^2 and Ca^2 ions, which is crucial for LPS integrity [35]. The fatty acid side chains also engage with LPS, enabling the secure insertion of polymyxin into the outer membrane. This interaction triggers a series of detrimental effects, including changes in outer membrane permeability, leakage of cell contents, and eventual bacterial cell death [29, 36]. Beyond inducing cytoplasmic leakage, this binding may neutralize the biological properties of endotoxins [14, 29]. Multiple hypotheses and models exist to explain the various mechanisms underlying polymyxin's bactericidal activity [13, 14, 29]. The principal pathways through which polymyxins exhibit their activity are shown in **Figure 2**.

2.4 Polymyxin resistance

The resistance of microorganisms to polymyxin remains incompletely understood, potentially arising from mutation or adaptation mechanisms [37, 38]. In most Gram-negative bacteria, the PhoP/Q and PmrA/B regulatory systems are pivotal in mediating polymyxin resistance. These systems oversee mechanisms that induce chemical modifications in the structure of bacterial lipopolysaccharides (LPS) (**Figure 3**).
In response to low levels of antimicrobial peptides, Mg+2 and Ca+2 ions, as well as other inducers such as low pH, excessive Fe+3, excessive Al+3, and phagosomes, these systems modulate resistance by altering the cationic charge of the cell wall. Cumulatively, these modifications reduce the negative charge of the bacterial outer membrane, resulting in a diminished affinity of polymyxin for the bacterial cell surface [29].

Modifying lipid A within the lipopolysaccharide (LPS) molecule, catalyzed by the gene products of pmrCAB and arnBCADTEF, is a fundamental mechanism underlying bacterial resistance to polymyxin antibiotics. These gene products play a pivotal

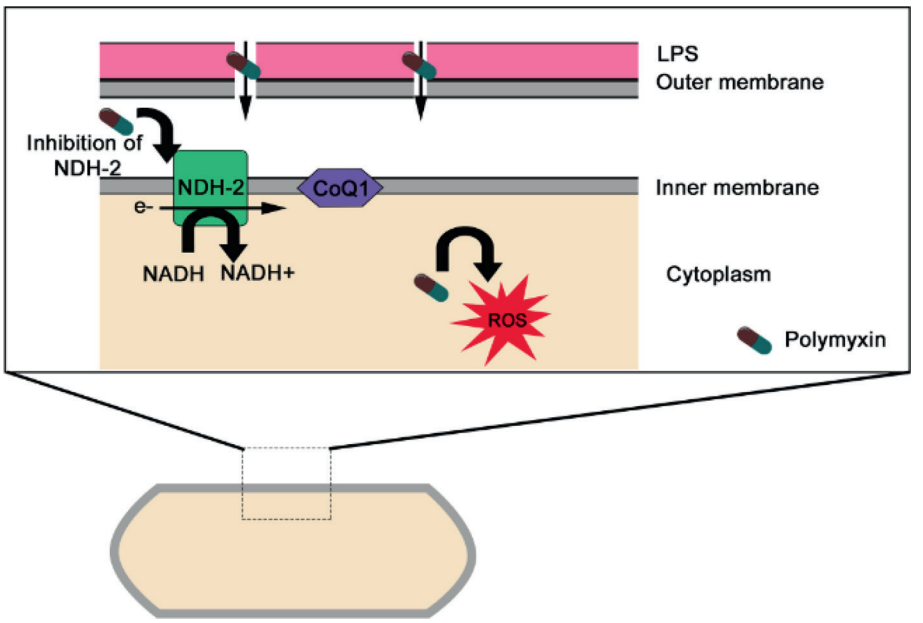

Figure 2.
Mechanisms of antibacterial activity of polymyxins in gram-negative bacteria. Disruption of the outer membrane, vesicle-vesicle contact, inhibition of respiratory enzyme NDH-2, and hydroxyl radical formation. CoQ1, coenzyme Q1.

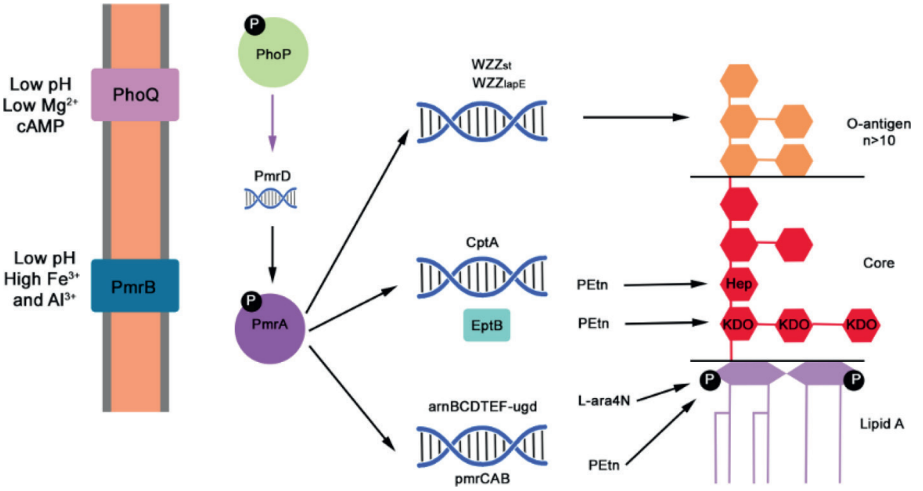

Figure 3.
Mechanism of polymyxin resistance changes in LPS. The PhoQP two-component system triggers pmrD expression. PmrD activates PmrA, cptA pmr, and the am operon. Working alongside EptB, CptA brings about modifications in the core polysaccharide of LPS. The pmr and am products facilitate the substitution of lipid a phosphates by Petn and L-ara4N, respectively. These collective alterations influence the charge of the outer membrane, resulting in polymyxin repulsion.

role in altering the surface charge and permeability of the bacterial outer membrane (OM) [39–41].

In *A. baumannii*, resistance development is primarily associated with changes in the LPS biosynthesis pathway. Currently, two mechanisms of polymyxin resistance

have been identified in *A. baumannii*. The initial mechanism involves the modification of lipid A *via* phosphoethanolamine and/or galactosamine, orchestrated by the PmrAB two-component system. Mutations at single nucleotide levels or elevated expression of pmrA (response regulatory protein) or PmrB (histidine kinase sensor) trigger the upregulation of pmrC, subsequently activating the production of phosphoethanolamine transferase (PEtN). This enzyme alters lipid A structure [42–46]. Other genes influencing LPS biosynthesis and lipid A configuration have also been documented. Additionally, the involvement of efflux pumps in colistin resistance cannot be dismissed [47, 48].

Another *A. baumannii* polymyxin resistance mechanism involves the complete loss of LPS from the outer membrane, which stems from mutations or inactivation due to the insertion of the ISAba11 insertion sequence into the lpxA, lpxC, and lpxD genes. These genes encode enzymes accountable for the initial stages of polymyxin LPS biosynthesis [43, 44, 49].

Mutations within the gene responsible for glycosyltransferase, a component involved in LPS biosynthesis, have also been linked to polymyxin resistance [50, 51]. According to current literature, both resistance mechanisms negate polymyxin-triggered bacterial death by obstructing the interaction of polymyxins with OM. The mechanisms are governed by the pmrCAB operon (for lipid A modification with PEtN), naxD (for galactosamine modification), or the lpx biosynthetic cluster (for LPS loss) [42, 44–46].

The outer membrane lipoprotein VacJ is an integral part of the Vps-VacJ ABC transporter system, responsible for maintaining the presence of phospholipids and LPS within the outer membrane [52]. Mutations within the vacJ and pldA genes could contribute to *A. baumannii's* colistin resistance due to their role in preserving the asymmetrical lipid distribution in the outer membrane [53]. In 2016, the discovery of the plasmid-borne mcr-1 gene marked the first instance of a colistin-resistant gene with horizontal transmission capability [54]. Unlike its predecessors, this gene can be disseminated via plasmids, expanding the reach of colistin resistance [55]. In subsequent years, the mcr-4.3 gene variant, carried by a plasmid, has also been identified [56–58]. Understanding the intricacies of polymyxin resistance mechanisms has become imperative for maintaining the effectiveness of this antibiotic until novel therapeutic alternatives are available. Nevertheless, assessing susceptibility to polymyxins remains a contentious issue as numerous laboratories do not employ the microdilution technique recommended for this evaluation [59].

2.5 Heteroresistence

Heteroresistance refers to the emergence of resistance to a specific antibiotic within a population initially sensitive to that antibiotic based on *in vitro* susceptibility test cutoff points [60]. Some studies describe this phenomenon without specifying the antibiotic concentration range. In contrast, others identify heteroresistance when subpopulations of an isolate grow at concentrations exceeding minimum inhibitory concentration (MIC) values found in susceptibility tests yet still within the susceptibility range [61, 62]. This variability in definitions, detection methods, and prevalence complicates understanding of heteroresistance's clinical significance [63]. This phenotype might represent a natural progression of antibiotic resistance, allowing bacteria to grow in the presence of antibiotics following resistance acquisition by most of the microbial population [63]. In 2006, Li et al. [61] first reported heteroresistance to colistin in multidrug-resistant *A. baumannii* isolates, defining it

as the emergence of resistance within a subpopulation of an otherwise susceptible (MIC ≤2 mg/L) group. Since then, this phenomenon has been widely observed, with prevalence ranging from 1.84–100% [64–66]. A related study showed higher heteroresistance in patients previously treated with colistin, suggesting prior colistin therapy might induce heteroresistance [64]. Additionally, the synergistic activity of colistin has been compromised when tested in antimicrobial combinations against heteroresistant carbapenem-resistant *A. baumannii* strains [67]. Findings regarding resistance stability within surviving subpopulations under nonselective conditions have varied across studies, implying a potential species-specific influence [60, 61, 64, 68]. Under colistin exposure, a subset of cells becomes colistin-dependent for optimal growth, indicating an adaptive response to colistin pressure and an intermediate stage between susceptibility or heteroresistance and full-blown colistin resistance [69, 70]. Hong et al. [60] found isolates displaying a heteroresistant phenotype at low antibiotic concentrations, distinct from the typical heteroresistant colistin isolates emerging at high colistin concentrations. The mechanisms of heteroresistance to colistin in *A. baumannii* are consistent with those previously described for colistin resistance, involving LpxACD, PmrCAB, and efflux pumps [60, 65, 68, 71, 72].

Detecting heteroresistant strains necessitates using the population profile analysis (PAP) method, the gold standard for identifying heteroresistance. In clinical practice, the introduction of the mini-PAP method, particularly for colistin with MIC >2 mg/L, has been recommended [73]. However, the fact that conventional susceptibility testing categorizes heteroresistant isolates as susceptible to colistin poses a notable concern [65]. Heteroresistance can sometimes be indicated by colonies within the growth inhibition zone, as seen with Etest® strips or disc diffusion assays. Nevertheless, standard dilution methods used for MIC determination fail to detect heteroresistance, potentially leading to suboptimal patient dosages. This suboptimal treatment might inadvertently select the resistant population, contributing to therapeutic failures [26, 74]. Inappropriate colistin use also holds significant potential for rapid resistance development and therapeutic inefficacy [75]. Under selection pressure, a subpopulation of resistant cells within a heteroresistant population can become predominant, yielding an entirely resistant population [68].

2.6 Clinical use

In clinical practice, polymyxins are employed as either polymyxin B or colistin. Despite their structural similarity, these drugs differ in their administered forms and exhibit distinct clinical pharmacokinetics (PK) [30]. Polymyxin B is directly administered in its active form as polymyxin B sulfate salt. In contrast, colistin is administered as an inactive prodrug called colistin metasulfate or colistimethate (CMS). Once metabolized, CMS is converted into the active ingredient colistin base. CMS is less toxic than colistin, and its conversion to colistin occurs gradually, coupled with rapid renal elimination.

Consequently, only about 20–25% of the administered CMS is effectively transformed into colistin [76–78]. Polymyxin B administration leads to quicker attainment of target concentrations [79]. Although polymyxin B and colistin exhibit comparable in vitro antimicrobial activity [30], differences in their plasma concentration profiles following therapy initiation will likely significantly impact their pharmacodynamic responses in patients.

3. Polymyxin toxicity

The 1990s saw the emergence of multidrug-resistant bacteria, including those resistant to β-lactams, aminoglycosides, and quinolones, causing nosocomial infections, particularly in intensive care units [80–83]. This scenario increased interest in polymyxins and spurred several reviews [84, 85]. These drugs' most significant adverse effects include nephrotoxicity, particularly acute renal failure, and neurotoxicity. The latter is thought to result from the high binding affinity of polymyxins to brain and renal tissues [86]. Additional effects encompass allergies leading to skin lesions resembling urticaria, pain at the injection site (with intramuscular administration), thrombophlebitis (with intravenous injection), fever, and eosinophilia [87, 88].

3.1 Nephrotoxicity

Nephrotoxicity ranks as the foremost adverse event often linked to the use of polymyxins. Thus, comprehending the mechanisms and risk factors for its development has been a focal point of research [89, 90]. Clinical manifestations of polymyxin-associated nephrotoxicity include direct toxicity to renal tubules leading to tubular necrosis, oxidative damage, decreased glomerular filtration rate, reduced creatinine clearance, and elevated serum urea and creatinine levels [80, 91]. Risk factors for kidney damage among polymyxin users encompass high doses, concurrent use of other nephrotoxic drugs, vasoactive medication requirements, and a higher body mass index [92–95]. The substantial concern with nephrotoxicity lies in its dose-dependent nature. In other words, the choice of therapy can influence the extent of drug-induced toxicity, potentially exacerbating the clinical condition of patients [96]. Dose-dependent nephrotoxicity is the most frequently reported adverse event with intravenous polymyxin use, affecting between 30 and 60% of patients [78, 85, 97–101]. However, it is often reversible [102]. While most studies have examined colistin, fewer studies have focused on polymyxin B. Due to the slower conversion of CMS to colistin, reaching therapeutic serum levels may be delayed, necessitating higher initial CMS doses to achieve effective treatment early on. However, this strategy is constrained by the potential for nephrotoxicity. Polymyxin B, administered directly in its active form, reaches the desired plasma concentration more promptly [30]. Recent literature suggests greater nephrotoxicity with colistin compared to polymyxin [103]. However, these findings require careful evaluation due to many factors influencing nephrotoxicity development, especially during the initial stages. Additionally, the potential nephrotoxicity of low polymyxin B doses may have been underestimated. Several studies have explored the efficacy of polymyxin B and colistin against *A. baumannii*, providing data on nephrotoxicity incidence and mortality (**Table 1**).

Acute kidney injury (AKI) is a prevalent clinical complication observed primarily in critical and hospitalized patients, characterized by the release of measurable proteins in both plasma and urine. This condition is rooted in the sudden decline of renal function, classified into risk, damage, failure, loss, and AKI stages [137, 138]. Critically ill patients suffering from AKI often face elevated mortality rates. This acute injury can progress to chronic kidney disease, defined by kidney damage and a glomerular filtration rate below 60 mL/min/1.73m^2 over 3 months. Therefore, discontinuing polymyxin therapy is imperative whenever signs of renal failure are detected. Supportive care, including monitoring fluid intake, output, and electrolytes, becomes necessary when renal dysfunction is associated with polymyxin use [85].

N° of patients/ therapy	GNB (n)	Definition of nephrotoxicity	Nephrotoxicity (%)	Mortality rate (%)	Ref.
60/COL	AB (39) PA (21)	CrL of 1.5 mg/dL or urea level of 50 mg/dL	27 (NRF) 58 (ABCL)	37	[104]
21/IVCOL	AB (21)	SCr value of 12 mg/dL, reduction in the calculated CLCr of 50% relative to the matter at antibiotic therapy initiation, or a decline in RF that resulted in the need for RRT	24	61.9	[105]
60/PB	AB (46) PA (2) AB + PA (2) NI (10)	Double the SCr for a value ≥2 mg/dL	14	20 57 (DRF) 15 (NDRF)	[106]
26/COL	PA (20) AB (6)	ND	14.4	33.3	[107]
16/IVCOL, AEROPB + AA	AB (16) PA (12)	Doubling of SCr	6	21 (EOT) 48 (AD)	[108]
19/IVCOL	PA (12) AB (5)	CrV at the beginning of COLtreatment was compared with the maximum value of creatinine during therapy as well as with the CrV at the end of treatment using a non-parametric test (Wilcoxon)	0	41.2	[109]
55/COL	AB (36) PA (19)	SCr value of 12 mg/dL, reduction in the calculated CLCr of 50% relative to the matter at antibiotic therapy initiation, or a decline in RF that resulted in the need for RRT	0	27	[110]
43/COL	PA (35) AB (8)	Acute RF was defined as a rise of 2 mg / dL in the SrCr level of patients with previously normal renal function	62.5	27.9	[111]
51/COL	AB (28) PA (23)	Normal renal function was defined as a SCr level of 1.3 mg/ dl or lower.	8	24	[112]
37/IVPB, PBVN, both (IPB/PBVN), DOXI	AB (37)	Increase in SCr of 0.5 mg/dL, or increase ≥50% in SCr or reduction of ClCr ≥50%	21/6	27	[113]
45/IVPB	PA (20) AB (19) PA + AB (2) NI (4)	Acute increase in SCr level by >0.5 mg/dL over 24 h	4	52 (IH)	[114]
16/PB	PA (8) AB (5) KP (3) EC (1)	Increase in SCr of 0.5 mg/dL or a 50% reduction in CLCr	55	63	[98]

N° of patients/ therapy	GNB (n)	Definition of nephrotoxicity	Nephrotoxicity (%)	Mortality rate (%)	Ref.
82/COL, PB	AB (82)	Doubling of SCr (any time during treatment compared with the start of therapy) or increase by 1 mg/dL if initial SCr was 1.4 mg/dL	26 (COl group) 27 (PB group)	56 (COL group) 61 (PB group)	[115]
114/IVPB	PA (95) AB (13) KP (1) PA + AB (2) NI (3)	Baseline SCr < 1.5 mg/dL when SCr levels increased to 1.8 mg/dL (AKI) or baseline SCr 1.5 mg/dL when SCr levels increased to >50%, or there was a need for dialysis	22 AKI/NS	61.4 92 (DAKI) 53 (NDAKI)	[116]
276/PB	PA (126) AB (86) NI (64)	MRI: 50% but <100% (increase in creatinine concentration during therapy); MORI: 100% (increase in creatinine concentration but with no need for hemodialysis); SRI: need for hemodialysis during therapy	15.7 (MRI) 38.3 (MOSRI)	60.5 (IH)	[99]
80/PB (NPD or CD)	KP (49) AB (21) PA (14) EC (4) ECO (1)	Defined by RIFLE criteria	40 (1 week after the last dose)	15 vs. 20 (EOT) 30 vs. 38 (EOH)	[116]
173/COL, PB	AB (107) PA (46)	Defined by RIFLE criteria	60 (COL group) 41.8 (PB group)	ND	[92]
32/IVPB	AB (26) PA (1) ECO (1) SE (1) Mu (3)	Defined by RIFLE criteria	18.7	28.1 (EOT)	[117]
225/IVCOL, PB	PA (103) AB (74) KP (52) ECO (11) Other (17)	Prevalence of nephrotoxicity within 30 days in colistimethate group compared with PB group Comparison of nephrotoxicity prevalence in matched patients	21.4 (COL group) 21.4 (PB group)	55.3 (COL group) 21.1 (PB group)	[93]
104/PB	AB (34) KP (25) PA (11) Mu (34)	Defined by RIFLE criteria	14.4	47	[118]
132/COL, PB	AB (43) PA (22) KP (12) DI (18) NI (37)	Classified according to AKIN criteria	20.8 (AKI/PB group) 38.9 (AKI/COL group)	47	[119]
36/PB	A spp. (12) KP (8) PA (6) ECO (6) E spp. (5) Other (9)	Increase of 100% of SCr level from baseline	21.4	44.5	[120]

N° of patients/ therapy	GNB (n)	Definition of nephrotoxicity	Nephrotoxicity (%)	Mortality rate (%)	Ref.
410/PB	AB (150) PA (45) KP (42) ECO (5) EA (5) NI or NR (162)	Defined by RIFLE criteria	12.7	42	[121]
151/ PB	KP (92) AB (32) PA (17) Other (10)	AKI: increase in SCr 1.5 times the value at PB initiation or the initiation of RRT by day 7 of PB treatment, defined by RIFLE criteria	35.8 AKI	NS	[122]
192/ IVPB	KP (92) AB (53)	Defined by RIFLE criteria	45.8	NS	[123]
491/IVCOL, PB	AB (180) KP (55) PA (51) EA (9) ECO (5) NI (190)	Incidence of AKI by RIFLE criteria	38.3 (COL group) 12.7 (PB group)	NS	[124]
291/PB, NVPT, in vitro VCT	AB (228) PA (61) KP (14) Other (7)	Defined by RIFLE criteria	98 of 291	23	[125]
112/IVCOL, PB	KP (31) AB (22) PA (19) ECO (5) NI (35)	A two-fold increase in SCr or a 50% decrease in estimated CLCr	26.8	NS	[103]
84/IVPB, PBM, PB/ CARB, CEFO/ SUL	AB (81)	MRI: decrease in baseline CLCr of 50% or doubling of baseline SCr in patients with normal renal function, or an increase of baseline SCr of 50% or decrease of CLCr of 20% in patients with abnormal baseline anal function	7.1 (RI)	48.8 (IH)	[126]
222/PB	AB (67) E (50) PA (15) Other (4) NI (86)	Defined by RIFLE criteria	46.3	60.3	[127]
273/PB	KP (108) PA (74) AB (77) ECO (22) Other (9)	Defined by RIFLE criteria	32	47 (ODD) 17 (TDD)	[128]

N° of patients/ therapy	GNB (n)	Definition of nephrotoxicity	Nephrotoxicity (%)	Mortality rate (%)	Ref.
183/IVCOL or ICOL, IVCOL/ ICOL	*Acinetobacter calcoaceticus-Acinetobacter baumannii* (Acb) complex (183)	Increase in SCr of ≥0.3 mg/ dL in 2 days or ≥ 50% in 7 days after COL treatment without other defined causes	13.3	19.1	[129]
250/COL + MERO	AB (197) AB+KP (1) NS (52)	Classified according to AKI criteria	30.8	41.6	[130]
39/IVCOL	PA (34) AB (5) EC (1)	Based on the ROC curve, the cutoff value of the colistin trough concentration that would predict nephrotoxicity was 2.02 mg/mL	47.6	33.3	[131]
87/COL	AB (73) NS (14)	Increase in the SCr level by at least 50% from the baseline after≥48 h	27.6	NS	[132]
50/COL		Defined by RIFLE criteria	54 (MIC ≤0.5 μg/mL	NS	[133]
25/IVCOL	AB (25)	Increase in SCr to ≥1.5- fold from baseline, decrease in the estimated CLCr to <75% from baseline, or requirement for RRT	20	40 (IH)	[134]
163/COL	A spp. (118) PA (32) KP (7) E spp. (6)	Followed by KDIGO classification: creatinine elevation of ≥0.3 mg/dL in 48 h or ≥ 1.5 times baseline creatinine in an interval of up to 7 days	46	17.8	[135]
101/COL	AB (101)	Defined by RIFLE criteria	52.6 (LD group) 20.5 (WLD group)	51.3	[136]

COL, colistin; PB, polymyxin; PBM, polymyxin B monotherapy; IVCOL, intravenously colistin; ICOL, inhaled colistin; AEROPB, aerosolized polymyxin B; IVPB, intravenously polymyxin B; TDD, twice daily dosing; NRF, normal renal function; ABCL, abnormal baseline creatinine levels; PBVN, polymyxin B via nebulization; NPD, new protocol design; CD, conventional dosing; NVPT, nonvalidated polymyxin therapy; VPCT, validated polymyxin combination therapy; CARB, carbapenems; CEFO, cefoperazone; SUL, sulbactam; DOXI, doxycycline; MERO, meropenem; AB, Acinetobacter baumannii; PA, Pseudomonas aeruginosa; KP, Klebsiella pneumoniae; EC, Enterobacter cloacae; ECO, Escherichia coli; E spp., Enterobacter spp.; EA, Enterobacter aerogenes; A spp., Acinetobacter spp.; E, Enterobacteriaceae; DI, dual infection; SCr, serum creatinine; CLCr, creatinine clearance; CrL, Creatinine level; CrV, Creatinine values; NI, none identified; MRI, mild renal impairment; NR, not request; NS, not stated; NRF, normal renal function; ABCL, abnormal baseline creatinine levels; DRF, Developed renal failure; NDRF, not developed renal falure; Mu, multiple; AERO, aerosolized; RI, Renal impairment; RF, renal failure; AD, at discharge; AA, antimicrobial agente; ND, not determined; EOT, end of treatment; IH, In-hospital; RIFLE, Risk, Injury, Failure, Loss of kidney function and End-stage kidney disease; EOH, End of hospitalization; AKI, acute kidney injury; AKIN, acute kidney injury network; ODD, Once daily dosing; TDD, twice daily dosing; DI, dual infection; MORI, moderate and severe renal impairment; DAKI, developed Aki; NDAKI, not developed AKI; RRT, renal replacement therapy; KDIGO, kidney disease improving global outcomes; LD, loading dose; WLD, without loading amount.

Table 1.
Studies report nephrotoxicity during polymyxin therapy against Acinetobacter baumannii.

3.2 Neurotoxicity

Neurotoxicity constitutes another undesirable consequence of polymyxin administration. Neurotoxicity related to polymyxins affects 7–27% of patients, with most cases involving concurrent renal failure [139, 140]. Symptoms of neurotoxicity encompass weakness, peripheral and facial paresthesia, ataxia, ophthalmoplegia, nystagmus, difficulty swallowing, and eyelid ptosis [88, 139–144]. Severe manifestations include muscle blockade leading to respiratory failure, often requiring ventilatory support for 10 to 48 hours [140, 141]. Typically, these symptoms decrease upon tapering or discontinuation of the drug. The administration of colistin triggers the activation of pro-inflammatory mediators within neuronal cells [145]. Research indicates that neurotoxicity entails a complex interplay of apoptotic and inflammatory pathways. Studies involving colistin treatment (15 mg/kg/day for 7 days) revealed significant mitochondrial dysfunction in central and peripheral nervous tissues [146, 147]. Similarly, exposure to colistin (200 μM/24 h) induced apoptosis in around 50% of neuronal N2a cells in mice [145]. Further exploration using Western blotting and immunohistochemistry demonstrated that colistin-induced apoptosis in N2a neuronal cells hinges on generating reactive oxygen species (ROS) and the mitochondrial pathway [145, 148, 149]. Interestingly, co-administration of neuroprotective agents, such as curcumin and minocycline demonstrated, *in vivo* efficacy against polymyxin-induced neurotoxicity [145, 149].

3.3 Skin hyperpigmentation

Although nephrotoxicity ranks as polymyxin B's most significant adverse reaction, another substantial side effect is skin hyperpigmentation. Polymyxin B induces this condition, which impacts psychological well-being and results in significant esthetic harm [150–158]. Cutaneous hyperpigmentation has been observed as a reaction to polymyxin B, affecting adults and pediatric and neonatal patients [151, 153–155]. According to cohort studies, the incidence of cutaneous hyperpigmentation attributed to this drug ranges from 8–15% [151, 152]. Cutaneous hyperpigmentation involves biochemical and immunological mechanisms, primarily associated with histaminergic receptors that stimulate melanogenesis, ultimately leading to melanin deposition in the dermis [150]. Typically, skin darkening manifests between the third and seventh days following the commencement of intravenous polymyxin B treatment. This phenomenon does not show significant disparities concerning light exposure or infection sites across patients [152]. Hyperpigmentation is often concentrated on the face and neck regions with higher melanocyte density, while the rest of the body remains unaffected during treatment [152, 154, 155, 159].

In some cases, discontinuing polymyxin B treatment reveals hyperpigmentation that can persist for months [150]. During the COVID-19 pandemic, polymyxin B treatment was administered to physicians with COVID-19 and secondary multidrug-resistant bacterial infections, resulting in hyperpigmentation on the head and neck [160]. This pigmentary disorder may be associated with AKI in critically ill COVID-19 patients [160]. Excessive accumulation of polymyxin B might contribute to aberrant hyperpigmentation in neonates and infants with immature renal function [153, 158].

4. Conclusions

In summary, this chapter presents a comprehensive review of the toxicity of polymyxins, which serve as the last resort for treating infections caused by carbapenem-resistant *A. baumannii*. The chapter begins by highlighting the current significance of *A. baumannii* as a challenging pathogen in healthcare settings, given its formidable ability to develop resistance through diverse mechanisms. Accordingly, it ranks as a high-priority microorganism for research and developing new antimicrobials. Despite their notable toxicity, polymyxins were re-introduced in the late 1990s due to escalating carbapenem resistance and limited alternative options. The chapter delves into the discovery and isolation of polymyxins, focusing on polymyxin B and polymyxin E (colistin) as the two varieties in clinical use. Their distinctive structural features enable interactions with cell membrane LPS, leading to membrane disruption through the cationic peptide ring's hydrophilic nature and the fatty acyl chain's hydrophobic characteristics. The emergence of polymyxin resistance is addressed, focusing on its occurrence through mutation or adaptation in Gram-negative bacteria. In *A. baumannii*, the resistance mechanism involves genes influencing LPS biosynthesis and lipid A structure.

Additionally, efflux pumps and the mcr-1 gene contribute to colistin resistance. The phenomenon of heteroresistance to colistin in *A. baumannii* is explored, emphasizing its reliance on the population profile analysis method for detection. This method, recognized as the gold standard, has revealed the presence of heteroresistance and its association with the previously discussed resistance mechanisms. Lastly, the clinical use of polymyxin B and colistin is outlined alongside their toxic effects. Nephrotoxicity is a prominent adverse event tied to polymyxin use, characterized by direct renal tubule toxicity and dose-dependent, often reversible effects. Most studies focus on colistin. One of its clinical complications is acute kidney injury (AKI). Neurotoxicity emerges as another unwanted effect, causing symptoms that generally wane with drug reduction or discontinuation. Severe cases might involve muscle blockade leading to respiratory failure. Furthermore, skin hyperpigmentation, a recognized reaction to polymyxin B, affects patients of varying ages through complex biochemical and immunological mechanisms.

Acknowledgements

This research was funded by the Carlos Chagas Filho Foundation for Research Support of the State of Rio de Janeiro/FAPERJ (#110.198-13) and the Brazilian Council for Scientific Research (CNPq, #467.488/2014-2 and 301744/2019-0). Funding was also provided by FAPERJ (#210.003/2018) through the National Institutes of Science and Technology Program (INCT) to Carlos M. Morel (INCT-IDPN).

Author contributions

Conceived and designed the experiments: K.R., T.P.G.C.; writing—original draft: K.R.; review and editing: K.R., S.G.D.-S.; funding: S.G.D.-S. All authors have read and agreed to the published version of the manuscript.

Conflict of interest

The authors declare no conflict of interest.

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