Infection and Drug Resistance

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REVIEW

Adverse Events and Drug Resistance in Critically Ill Patients Treated with Colistimethate Sodium: A Review of the Literature

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Abstract: The adverse events related to sodium colistimethate have had variability regarding the prevalence of nephrotoxicity, neurotoxicity, and less frequent respiratory depression. In recent years, its use has been relevant due to the increase of multidrug-resistant bacteria since it is considered the last-line drug, being its main adverse event and reason for discrepancies between authors' nephrotoxicity. The indiscriminate use of antibiotic therapy has generated multiple mechanisms of resistance, the most common being related to Colistin, the bactericidal escape effect. Based on the search criteria, no randomized clinical trials were identified showing safety and efficacy with the use of Colistin, inferring that the application of the appropriate dose is governed by expert opinion and retrospective and prospective observational studies, which confounding factors such as the severity of the patient and the predisposition to develop acute renal failure are constant. In this review, we focus on identifying the mechanism of nephrotoxicity and bacterial resistance, where much remains to be known.

Keywords: colistin, colistimethate, nephrotoxicity, neurotoxicity, resistance mechanism, multidrug-resistant gram-negative bacteria, risk factors, high doses, toxicity

Introduction

Polymyxins were described in 1947[1,2] in isolates of *Bacillus Polymyxa*, subspecies *coelestinus koyama*.[1,3] Sodium colistimethate (CMS) was discontinued in the 1980s due to adverse events such as nephrotoxicity and neurotoxicity, and the marketing of new drugs with a higher safety profile. The lack of efficacy of the new drugs and the indiscriminate use of antibiotics made it an ideal environment for developing multidrug-resistant gram-negative bacilli (BGN-MDR), making their reintroduction feasible two decades later.[2,4]

These drugs are cyclic polypeptides whose primary mechanism alters the permeability of the lipopolysaccharide wall of gram-negative bacteria. In the literature, alternative mechanisms are described as the vesicle–vesicle contact route causing exchange and loss of phospholipids and the route of death by hydroxyl radical, given by the reaction of Fenton (hydrogen peroxide oxidizes ferrous iron in serum iron). This reaction generates oxidative damage leading to cell death.[4,5] Its antimicrobial spectrum comprises; A *cinetobacter baumannii, Pseudomonas aeruginosa, and K. pneumoniae*, having no activity against gram-positive bacteria since it does not bind favorably to lipoteichoic acid.[6]

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Its use should be reserved as a last-line drug when you have an infection with the bacteria mentioned above and under certain conditions as empirical treatment.[7]

We investigate the landscape of nephrotoxicity in the last decade and describe the various resistance mechanisms reported. Until now, it has been considered the last available antibiotic therapy against multi-resistant bacteria. However, during the COVID-19 pandemic, the use of colistin increased due to a lack of evidence of a standardized treatment, resulting in greater antibiotic resistance. Starting from this point, this review will allow more information about renal deterioration and resistance mechanisms associated with this drug in multiple studies.[8]

In one of the largest cohorts conducted before the period of his detention by Koch[9] in 1970, evaluated 317 patients using CMS, 63 (20.1%) developed acute kidney injury, while the development of neurological symptoms was in 23 (7.2%) of 317, being one of the *Falagas* hypotheses[10] that the increase in nephrotoxicity at that time was due to the use of CMS in intramuscular forms intravenously, as well as the development of adverse events that are currently infrequent, described in Figure 1. [27]

Resistance is one of the biggest concerns worldwide due to the lack of new drugs with equal or greater efficacy and fewer adverse events. The primary mechanism of resistance is the modification of 4-amino-4-deoxy-L-arabinose (L-Ara4N).[11]

The warnings of the Institute of Clinical and Laboratory Standards (CLSI) issued in the manual M100 version 32 concern limited clinical efficacy according to clinical data, pharmacokinetics, and pharmacodynamics (PK/PD), promulgating intermediate cohort point (<2 mg/dl) and resistant (>4 mg/dl).[12] To reduce the prevalence of nephrotoxicity, an adjustment of CMS to renal dose, proposed by the International Colistin Consensus, was made,[13,14] which to this day are still the guidelines used; however, the different clinical contexts, such as the patient in critical condition, mean that the doses proposed by the consensus do not reach the expected therapeutic efficacy.

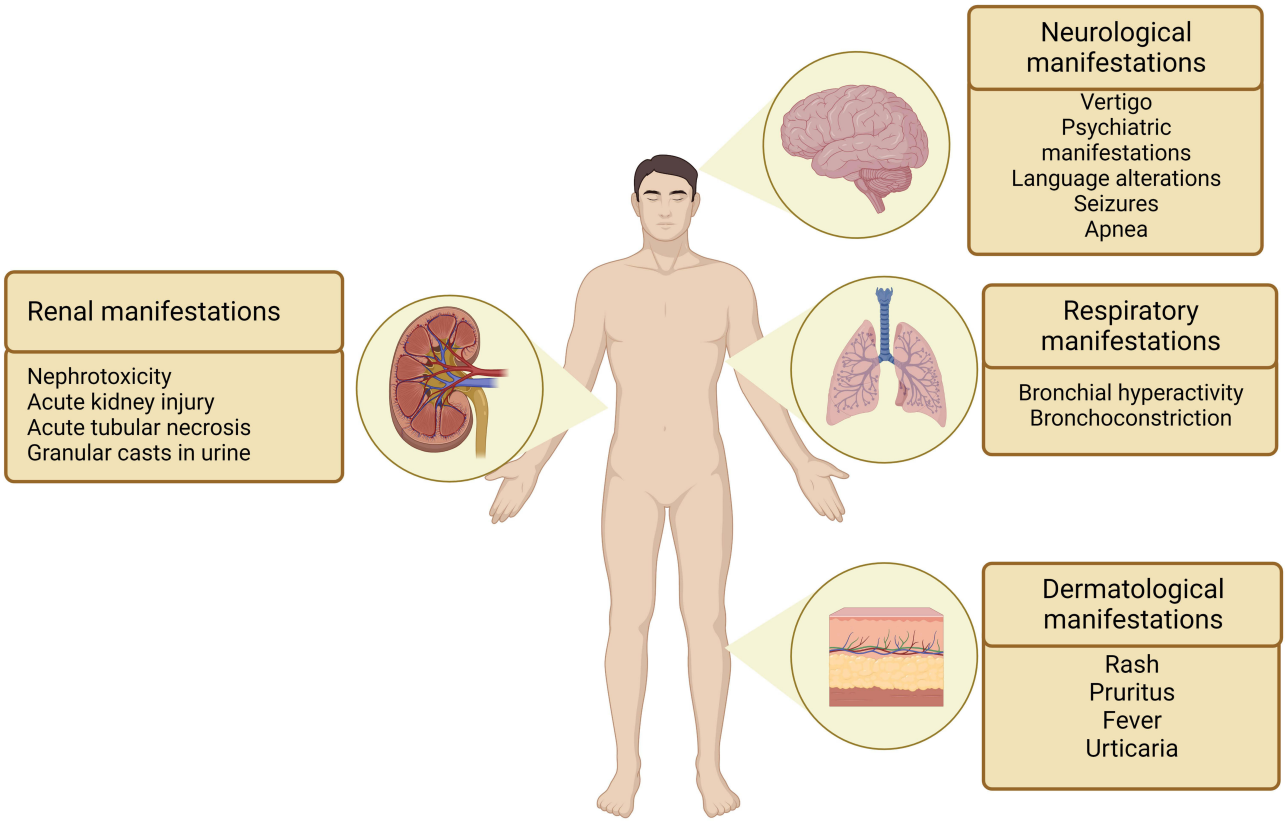

Figure 1 Adverse events related to colistin. Created with BioRender.com.

The lack of precise data on the prevalence of AKI due to the use of colistin in the last decade and of randomized clinical trials on the efficacy of Colistimethate sodium in critically ill patients also allows knowing the incidence of adverse events found today generated the need for a comprehensive review to obtain updated information on the use of colistin; therefore, the main objective of this review is to present a comprehensive and up-to-date overview of adverse events and resistance to the use of colistin in critically ill patients.

Materials and Methods

We searched for original articles, and reviewed articles in PubMed, Google Scholar, and Cochrane Library between Mar 15, 2022, and Jun 20, 2022, with a temporality from 2006 to 2022, in English or Spanish. The following search terms were used: "Colistin", "colistimethate", "nephrotoxicity", 'neurotoxicity', "resistance mechanism", "Multidrug-resistant gram-negative bacteria", "Risk Factors" "Toxicity", "High doses". Recommendations of the prism group were followed in terms of identification, detection, eligibility, and inclusion criteria. The authors evaluated the titles and abstracts of the studies according to the objective of the work. The inclusion criteria for the studies were:

- Prevalence of nephrotoxicity.
- Adverse events and mechanisms of nephrotoxicity.
- Mechanism of resistance from in vitro studies.
- Colistimethate mechanism of action.

Results

We identified 120 articles, of which 51 were eliminated for not meeting the inclusion criteria described above; of the 69, 14 were used for collecting prevalence with temporality from 2010 to 2022, and the rest were used for describing adverse events and resistance mechanisms (Figure 2). Acute kidney injury due to Colistin, resistance mechanisms, and exceptional adverse events such as neurotoxicity were identified in the included studies (Figure 1). According to the GRADE guide[15] Assessing the evidence quality was low because they had an observational design.

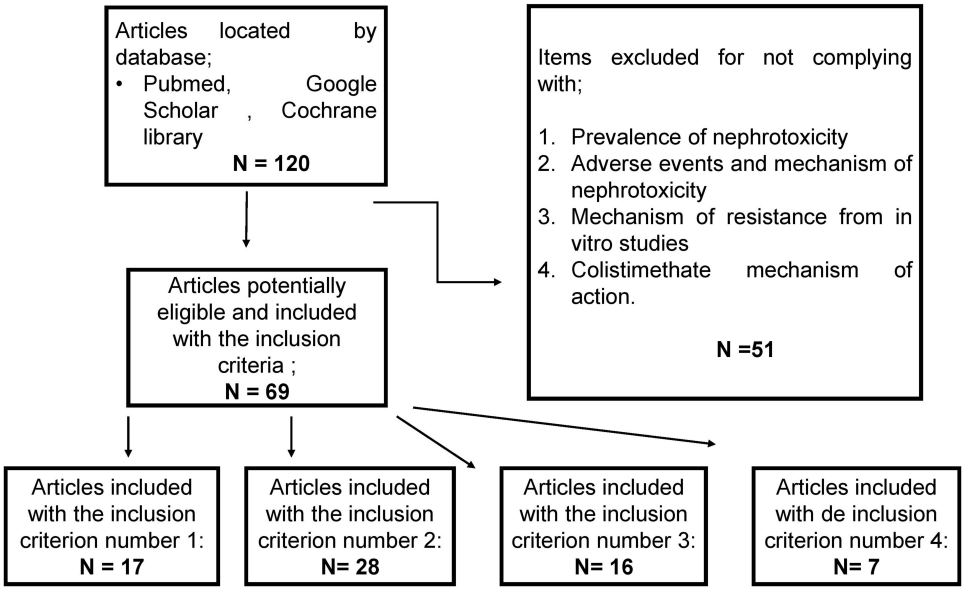

Figure 2 The article search and selection flowchart is summarized.

Prevalence and Incidence of Adverse Events

In 2020, Rosas et al[16] was the first study to mention the incidence of nephrotoxicity, which included 90 patients with a mean duration of treatment of 8.3 days and an incidence of 1.73 cases/100 days of treatment. Emphasizing that nephrotoxicity was transient and not an established lesion. Currently, in 2021 the meta-analysis conducted by Khalid Eljaaly et al.[17] Despite using established doses, they conclude that despite being a last-line drug, having some alternative would be more favorable to prevent the development of nephrotoxicity (Table 1). Martínez y cols[18] in 2014, in 2014, analyzed the prevalence of nephrotoxicity in critical patients, using RIFLE, concluding that critical patients may be more susceptible to nephrotoxicity,[19] contrasting with studies where the prevalence of kidney injury was lower in critically ill patients.[20,29,31]

In Mexico, Meraz Muñoz[20] in 2018, a retrospective cohort study of patients with MDR infection treated with CMS over four days evaluated whether the effect of AKI induced by CMS could have permanent damage at the renal level. Finding that of 29 patients who had colistin-associated AKI, after six months, 22 (75%) progressed to CKD (Grade 3). Concluding that acute kidney injury associated with Colistin had an increased risk of developing chronic kidney disease in 6 months.

Nephrotoxicity Criteria

According to the Kidney Disease guidelines: Improving Global Outcomes (KDIGO), 1) increase in serum creatinine by ≥0.3 mg/dl within 48 hours, 2) increase in serum creatinine to ≥1.5 times baseline, which is known or assumed to have occurred within the previous seven days, and 3) urine volume <0,5 mL/kg/h during >6 h.[21,22,69]

Molecular Nephrotoxicity Hypothesis

Suzuki[23] He described the first experimental evidence where CMS exerts its nephrotoxic effect by accumulating in proximal tubule cells. Determining that these cells reabsorb CMS by binding to megalin, a 600 kDa glycoprotein expressed in the apical membrane of the proximal tubule. Biological models showed a reduction in renal accumulation and a simultaneous increase in urinary excretion of Colistin when administered with a megalin-releasing agent (maleic acid) and megalin ligands

Table 1 Compilation of Nephrotoxicity Prevalence

Author	Year	Type of Study	Number of Patients	Adverse Event and Prevalence
Nittha Arrayasillapatorn[47]	2021	Retrospective Cohort Study	412 patients	Acute kidney injury 68.5%
Khalid Eljaaly et al[17]	2021	Meta-analysis	377 patients	Acute kidney injury 36.2%
Rosas et al[16]	2020	Retrospective, observational unicentric study	90 patients	Acute kidney injury 15.56%
Meraz Muñoz et al[20]	2018	Retrospective cohort study	72 patients	Acute kidney injury 40%
Abdellatif et al[48]	2016	Single-blind randomized study	149 patients	Acute kidney injury 39.4%
Joshua D hatzell et al[49]	2015	Retrospective study	66 patients	Acute kidney injury 45%
Martínez et al[18]	2014	Observational prospective study	104 patients	Acute kidney injury 47%
Tuon FF et al[50]	2014	Retrospective cohort study	132 patients	Acute kidney injury 38.9%
Sorli L et al[51]	2013	Prospective Observational Cohort Study	102 patients	Acute kidney injury 25–49%
Rocco M et al[52]	2013	Retrospective cohort study	279 patients	Acute kidney injury 40%
Dalfino L et al[53]	2012	Prospective study	28 patients	Acute kidney injury 17.8%
Pogue JM et al[54]	2011	Retrospective cohort study	126 patients	Acute kidney injury 43%
Andrew Deryke et al[55]	2010	Retrospective cohort study	30 patients	Acute kidney injury 33%
Paul M et al[56]	2010	Prospective cohort study	495 patients	Acute kidney injury 15.1%

(cytochrome c and FRALB). Yoshihisa Hori and Nobumasa Aoki, by cilastatin, suppressed megalin-mediated tubular reabsorption, thereby decreasing the nephrotoxic effect.[24,25]

Nezu and Tamai et al.[26] Investigated that the mutation in the SLC22A5 gene located on chromosome 5q31.1 causes a systemic deficiency of carnitine, showing that a single intraperitoneal administration of Colistin did not produce signs of renal damage (Figure 1).[27]

Mohammad Tabish[28] described one of the less common causes found in the literature as acquired Bartter syndrome induced by Colistin, using three days of standard therapy in the patient, a 46-year-old man, which remitted upon discontinuation of the drug.

Neurotoxicity

So far, there is no precise neurotoxicity mechanism, and there are only a few reports of neurological damage in patients treated with this drug.[10,29] Nevertheless, Jeong ES et al[30] and collaborators agreed with Falagas et al[10] theory, where before stopping the drug, there was no pre-established dose. Intramuscular doses were used in intravenous forms, having this longer half-life and higher concentration in cerebrospinal fluid (CSF). Due to intrathecal administration, when plasma concentrations exceed the dose of 10 mg/day or greater than 20 mg/day, the generation of chemical meningitis is observed with a prevalence of 10 to 20%, developing meningismus, fever, altered mental status, increased leukocyte count and decreased glucose levels in the CSF (liquefied pleocytosis).[31,32]

Resistance Mechanism

The resistance mechanisms in Gram-negative are complex and only fully understood now.[33] The most accepted theory is the bactericidal effect's escape by reducing the outer membrane's negative charge, which hinders binding to Colistin.[11] The molecular mechanism that is described by replacing the phosphate groups of lipid A by the cationic remains of 4-amino-4 deoxy-L-arabinose (L-Ara4N) or phosphoethanolamine (PEtN), mutations in the regulatory systems PhoPQ and PmrAB can lead to increased positive regulation, which is accompanied by the addition of more cationic residues to LPS, decreasing the membrane load, and therefore avoiding colistin action.[34]

The regulations of enzymes are in charge of the system operate pmrCAB encoding three functional proteins 1) pEtN phosphotransferase Pmrc (eptA) having as function the cationic addition to lipid A. 2) Regulator of response PmrA (BasS) function: once activated, allows the activation of the operon pmrCAB, operon pmrHFIJKLM and the gene pmrE, these last two responsible for the synthesis of L-Ara4N and its binding to lipid A. 3) protein kinase sensor PmrB Function:

Activates PmrA through phosphorylation. PhoP (PhoQ), PmrA (PmrB) sensor kinases detect a reduction in the magnesium and calcium contents of the cell envelope, in addition to the presence of Colistin, so the presence of expression of these.[35,36]

PhoQ and PmrB drive phosphorylation of response regulators (PhoP and PmrA), enhancing the binding of these regulators to the promoters of regulated genes, generating transcription of several genes, including PmrD, its stabilized product PmrA in its phosphorylated state, allowing the generation of L-Ara4N (Table 2).[11,36]

Other Adverse Events

Nephrotoxicity, neurotoxicity, lung damage, dermatological lesion are the main adverse events reported (Figure 1). At the pulmonary level, the administration of colistin for nebulization can cause different degrees of hyperreactivity, such as dry cough or bronchoconstriction. While at the dermatological level, there have been cases of rashes, rash, pruritus, urticaria or fever (Figure 1). [4]

Table 2 Compilation of Resistance Mechanisms

Bacteria	Membrane Modifications	Resistance Mechanism
Klebsiella pneumoniae	Modifications of the rest of LPS	L-Ara4N y/o PEtN modification of lipid A.[57]
	Overproduction of capsular polysaccharide	Operon overexpression PhoPQ.[58]
	Efflux Pump System	Operon overexpression pmrAb.[59]
	Bacterial barrier permeability regulator	Regulator RamA.[60]
Acinetobacter Baumanii	LPS fraction modifications	L-Ara4N.[61]
	Loss of LPS	Influence of operon expression pmrCAB.[62,63]
	Membrane Fluidity/permeability	Lipid deacylation A.[64]
	Efflux Pump System	Abolition of limpid A.[65]
	Heteroresistance	Mutatión lpxA, lpxC, lpxD in acid medium.[66]
Pseudomonas Aeruginosa	Modification of the LPS fraction	Multi-drug efflux pump and LPS additions in response to Zn 2+.[67]
	Loss of LPS	Inactivation of lipid A biosynthesis[67,68]
	Unclear Efflux Pump System	Multi-drug efflux pump.[62,64]

Discussion

His literature review focused on determining the prevalence of the last twelve years of CMS and the development of nephrotoxicity, as well as describing the various mechanisms of resistance to this drug, the latter being one of the leading public health problems worldwide.

Martinez et al[18] found that the prevalence of nephrotoxicity with the use of CMS from 2010 to 2022 ranged (from 15.1% to 68.5%), of which the highest percentage is represented in critical patients; in this type of patents; the authors described that the predisposition to acute kidney injury is due to the use of invasive mechanical ventilation, polypharmacy, hydro electrolytic alterations, acid-base state, the latter being a component of the hypothesis of Falagas et al[10] ten where he relates a state of acidosis with a decrease in bactericidal activity, not being able to reach the minimum inhibitory concentration (MIC) <2 this,[12] given the neutral pH characteristics of the lipopolysaccharide[2,3,10] However, up to now, there is no evidence of this deregulatory mechanism.

The sars-cov2 pandemic had a significant increase in patients in critical condition, so the use of CMS increased considerably due to the irrational use of antibiotics and the latent generation of multidrug-resistant bacteria, this added to the various variables existing in each patient, such as race, age, sex, state of severity, biochemical alterations (hypoalbuminemia), sepsis, septic shock,[18,19,21,45] which may contribute to an increase in the nephrotoxic potential of CMS,[21,22] since it has been described that they predispose to the risk of acute kidney injury, so that, currently, the assessment of these variables could decrease the incidence of acute kidney injury.

One of the theories of nephrotoxicity generation proposed by Rosas et al[16] agrees with retrospective and prospective studies,[17,18,20,21] in those patients in which the use of loading doses and duration of treatment, not schematized, generates the development of acute renal injury due to the effect of accumulated dose, so the acceptable use to reach a minimum inhibitory concentration (MIC) requires knowledge beyond the stipulated guidelines. The expertise and individualization of the patient are fundamental tools to have the desired therapeutic effect.

In the retrospective cohort of Katip et al,[37] 396 patients with infections caused by *E. coli and Klebsiella pneumoniae* were studied to evaluate the mortality by dose load of colistin. Compared to the carbapenem group, nephrotoxicity induced by colistin was reported at 48.2%; this group had more significant mortality at 30 days, greater clinical failure, and bacteriological failure. Meanwhile, what was studied by Katip et al,[38] in the retrospective cohort of 365 patients, who evaluated the clinical efficacy and nephrotoxicity of colistin alone versus colistin with vancomycin, found that the

colistin alone developed nephrotoxicity in 49.24% and 48, 96% with colistin and vancomycin. However, the results did not show significant differences in the clinical, microbiological, and nephrotoxicity response between more vancomycin vs colistin groups. Katip et al[39] conducted a retrospective cohort study at Chiang Mai University Hospital, where they studied a total of 383 patients to evaluate 30-day survival, as well as determining nephrotoxicity in critically ill patients who received a No-loading dose (LOD) versus LD of CMS for the treatment of carbapenem-resistant *A.baumannii* (CRAB) infection, resulting in 1.70 times greater survival than those who did not use loading doses.

Meanwhile, the nephrotoxicity of colistin with a loading dose was 56.76%, while using colistin without a loading dose generated 32.26% of nephrotoxicity. The loading dose mechanism was the main factor in the generation of nephrotoxicity.

The future projection for the early detection of nephrotoxicity is the biomarkers of renal damage, as described by some authors,[40–44] determine that Cystatin C (Cys C) is the biomarker of choice over NGAL and α-1-microglobulin for the early detection of AKI. In addition, mathematical models have been described; one of them is Phe, which has a high percentage of specificity, another is the CART analysis with high sensitivity, and these could be applied during treatment with CMS, so we can establish that these would allow the development of preventive measures.

One of the world health problems is the emergence of multidrug-resistant gram-negative bacteria, the main ones being: *Pseudomonas aeruginosa, Acinetobacter baumannii, and Klebsiella pneumoniae*.[38]

The lack of new antibiotics to combat these pathogens makes using CMS more frequent. Even with the existence of the dosage recommended by the International Colistin Committee,[12] the bactericidal effect has a narrow therapeutic margin that is often related to the prescription of lower doses, thus predisposing to trigger one of its primary mechanisms such as "bactericidal escape" which through the reduction of negative charge and L-Ara4N modification generates resistance,[45] other mechanisms that are described less frequently are lipid A deacylation, permeability and loss of lipopolysaccharide,[54–57] which are also triggered by under-therapeutic exposure.

Currently, Xu et al[46] observed the natural resistance to Colistin by eptA genes of *Neisseria meningitidis*, describing the beginning of knowledge on new forms of resistance, being the main public health problem for being the last pharmacological line, physicians and pharmacists must evaluate the determination of the therapeutic efficacy of colistin since it has a narrow therapeutic margin. Mainly based on its pharmacodynamic profile since nephrotoxicity and resistance is concentration dependent. Therefore, the ratio between the area under the curve and the MIC (AUC/MIC ratio) is the best PK-PD parameter to reflect the efficacy profile of colistin. In most hospitals in Latin America, therapeutic efficacy monitoring is evaluated by taking periodic cultures or reducing the number of leukocytes. Starting from this point, it can be just as cost-effective as the AUC/MIC ratio for decision-making. Giving guidelines that colistin should not be prescribed in monotherapy, given the high rate of in vitro resistance of multiple genes, including the *mrc-1* gene.[54,55]

These data provide evidence to recommend combining colistin plus carbapenems since they have been associated with less nephrotoxicity. In addition, they reach the appropriate minimum inhibitory concentration, thus avoiding further therapeutic failure and antibiotic resistance.[37–39]

Meraz et al[20] carried out a study in Mexico, proving the irreversible damage caused by CMS, in which they found that up to 75% of the patients evolved to chronic renal disease within six months.

However, they do not describe whether there was any association with sepsis, which is always a distracting factor in various studies and can bias the validity of the data obtained.

In this sense, this finding contributes to some theories generating uncertainty about the progression of chronic kidney disease. Clinical verification is required in these cases of irreversible damage.

We acknowledge the limitations of our review. One of the main points was the loss of homogenization of the various study cohorts due to the variation in the characteristics of the patients on therapy and the frequent presentation of sepsis, knowing that it is a factor that by itself can cause nephrotoxicity.

Conclusion

The frequency of adverse events, and mainly nephrotoxicity associated with Colistin, has a wide range of predisposing variables, including population conditions, patient severity, sepsis, mechanical ventilation, age, and other factors. However, its molecular mechanism still needs to be well defined.

The frequency of adverse events, and mainly nephrotoxicity associated with Colistin, has a wide range of predisposing variables, including population conditions, patient severity, sepsis, mechanical ventilation, age, and other factors. However, its molecular mechanism still needs to be well defined.

So far, its efficacy rate ranges from 50 to 79.1%, this being the primary justification of most authors for its use. Still, the very narrow therapeutic margin makes the possibility of nephrotoxicity a latent adverse effect and underestimating the dosage to prevent it may be the trigger effect to unleash resistance. The lack of a randomized clinical trial is the paradigm for the safe use of the drug.

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Disclosure

Victor Hugo Ahumada Topete and Kevin Jesus de Dios Sanchez are co-first authors for this study. The authors declare that they have no conflict of interest in this work.

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