Research Article

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Colistin Nephrotoxicity in The Critically Ill Patient

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ABSTRACT

Background: The kidney is a major drug excretion organ and is therefore exposed to high concentrations of potentially toxic drugs. Nephrotoxicity is defined as a rapid deterioration of kidney function due to the toxic effect of drugs and chemicals. Colistin is a polymyxin-type antimicrobial currently used to treat multidrug-resistant gram-negative infections.

Methodology: A systematic review was carried out through various databases from January 2014 to February 2022; The search and selection of articles was carried out in indexed journals in English.

Results: Colistin is a cationic polypeptide antibiotic with a cyclic structure that belongs to the group of polymyxins. One of the criteria or scales to quantify colistin nephrotoxicity, which is still being used and implemented in clinical practice, are the RIFLE criteria. The main clinical characteristics of colistin nephrotoxicity are: Elevated serum creatinine, Oliguria, Increased fractional excretion of sodium, microscopic haematuria, Mild proteinuria, Hypoalbuminemia.

Conclusion: This review offers updated and detailed information on the main quantification criteria of colistin-associated nephrotoxicity as well as the main markers of colistin-associated renal injury, in order to establish more appropriate care behaviours.

KEYWORDS: Nephrotoxicity, Colistin, ICU, Antibacterial

INTRODUCTION

The majority of patients in critical condition become drug dependent until they reach a state of resolution of the acute pathology they are undergoing. Therefore, the care of these patients must be carried out in a specialized and trained unit, such as the Intensive Care Unit. In this unit, high proportions of personnel can

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be offered, in order to care for the critically ill patient, providing advanced monitoring and organ support in order to improve the morbidity and mortality of patient [1]. The kidney is a major drug excretion organ and is therefore exposed to high concentrations of potentially toxic drugs. To date it is known that nephrotoxicity caused by drugs is responsible for approximately 20% to 60% of cases of acute renal failure in hospitalized patients, being associated with increased mortality and morbidity in both children and adults [2]. Nephrotoxicity is defined as a rapid deterioration of kidney function due to the toxic effect of drugs and chemicals. There are several ways, and some drugs can affect kidney function in more than one way [3]. Antibiotics play an important role in different pathologies, either to eradicate and/or control the pathogen and also as a prophylactic method. Antibiotics belong to the class of drugs most prescribed worldwide, so antibiotic-associated nephrotoxicity is widespread. A wide range of antimicrobial agents have been associated with nephrotoxicity, but the characteristics of renal injury vary depending on the agent, its mechanism of injury, and the site of toxicity within the kidney [4]. Colistin is a polymyxin-type antimicrobial currently used to treat multidrug-resistant gram-negative infections caused by bacteria such as Acinetobacter Baumann, Pseudomonas aeruginosa, and Klebsiella pneumoniae. This antibiotic had its beginnings in the year 1950, but it fell into disuse due to the nephrotoxicity caused, but due to the great resistance of some microorganisms, its importance has recently increased [5]. Distinguishing nephrotoxicity caused by an antimicrobial agent from other potential triggers is important to facilitate both early recognition of drug toxicity and prompt discontinuation of the offending drug, as well as to avoid unnecessary interruption of therapy [6,7]. Like the manifest fear about the high risk of nephrotoxicity, which still prevails among prescribers; it can lead to colistin underdosing, treatment failure, and the development of colistin resistance [8]. Therefore, it is convenient to carry out this work, in order to provide updated and detailed information on the main quantification criteria of colistin-associated nephrotoxicity as well as the main markers of colistin-associated renal injury.

MATERIALS AND METHODS

A systematic review was carried out, the articles were chosen in English from the PubMed, Schiele and ScienceDirect databases, among others. The collection and selection of articles was from the years 2014 to 2022. As keywords, the terms were used in the databases according to the Dec's and Mesh methodology: Nephrotoxicity; Colistin; ICU; Antibacterial. 103 original and review publications related to the subject studied were identified, of which 28 articles met the specified inclusion requirements, such as articles that were in a range of not less than the year 2014, that they were full text articles and to report on the subject. As exclusion criteria, it was taken into account that the articles did not have sufficient information and that they did not present the full text at the time of their review.

RESULTS

Antimicrobial and Colistin Resistance

Colistin is a cationic polypeptide antibiotic with a cyclic structure that belongs to the group of polymyxins. Previously, it was used with a higher frequency than it is today, but due to the great risk of developing nephrotoxicity in close to 50% of patients and neurotoxicity, its clinical use has fallen into disuse [9]. But due to the number of resistant pathogens, such as carbapenem-resistant Acinetobacter Baumann, Pseudomonas aeruginosa, and Enterobacteriaceae, its implementation is once again increasing in clinical practice [10]. In the ICU we find many risk factors that contribute to the pathogens acquiring resistance, within these factors we find the implementation of mechanical ventilation, administration of intensive pharmacological therapy as well as the performance of other invasive procedures, increasing the risk of infections acquired in hospital, as well as mortality rates [11]. It is believed that 25% of hospital-acquired infections occur in the intensive care unit. The frequency of hospital infections and susceptibility to antibiotics may vary from country to country, from hospital to hospital, and within different units of the same hospital [12]. The reduction in the resistance of patients being monitored in the ICU, long-term hospitalization, mechanical ventilation, and invasive procedures such as catheterization lead to an increased incidence of infections in these units. Multiple antimicrobial resistances occur with the widespread use of broad-spectrum antibiotics in these units.

Criteria for the Quantification of Colistin-Associated Nephrotoxicity

Table 1: RIFLE criteria.

Category	Criteria
Risk (R)	Increase in creatinine level x1.5 or decrease in GFR >25%
Injury (I)	Increase in creatinine level x2 or decrease in GFR >50%
Failure (F)	Increase in creatinine level x3, decrease in GFR > 74% or creatinine level > 4 mg/dl
Loss (L)	Persistent acute renal failure or complete loss of function for >4 weeks
End-stage renal disease (E)	End-stage renal disease for >3 months

One of the criteria or scales to quantify colistin nephrotoxicity are the criteria for risk, injury, failure, loss, and end-stage renal disease (RIFLE), for its acronym in English Risk, Injury, Failure, Loss, ESKD. end-stage renal disease). This is considered a valuable validated tool for the assessment of acute kidney injury based on both the change in glomerular filtration rate and serum creatinine concentration. In Table 1 we can identify the classification [13,14]. Although we can find other important classifications, such as the AKIN classification (Acute Kidney Injury Network); Table 2.

Table 2: AKIN stage and criteria.

Ira Stadium	Criteria
AKIN-I	Increase in SCr greater than or equal to 0.3 mg/dL or 1.5-2.0 fold increase in SCr over baseline SCr
AKIN II	>2.0 - 3.0 increase in SCr from baseline SCr
AKIN-III	Increase in SCr >3.0 from baseline or Increase in SCr >4 mg/dL with an acute increase of at least 0.5 mg/dL or need for renal replacement therapy

Higher scores in both the AKIN and RIFLE classification have been found to be associated with higher ICU mortality. The definitions of RIFLE and AKIN have a high concordance in staging the severity of acute kidney injury. But the AKIN definition has shown greater sensitivity compared to RIFLE, since it encompasses a larger number of patients who are at risk of acute injury. Being this greater sensitivity the original intention of AKIN. Both definitions

are capable of predicting dialysis requirement, as well as ICU and 28-day mortality. There is another classification to identify kidney damage, it is the KDIGO classification, it is currently the most widely used due to its high sensitivity and specificity when associated with other criteria (Table 3).

Table 3: KDIGO classification.

Kidney Function Category	FG (ML/MIN/1.73 M2)	Terms
G1	≥90	Normal or high
G2	60-89	Slightly diminished
G3a	45-59	Mild to moderate decrease
G3b	30-44	Moderate to severe decrease
G4	15-29	Severe decline
G5	<15	Kidney failure (G5D, is treated with dialysis)

Nephrotoxic Mechanism

The kidney is a major drug excretion organ and is therefore exposed to high concentrations of potentially toxic drugs. Drug-induced nephrotoxicity is a common and potentially serious complication of drug administration that occurs in both hospitalized and outpatient settings [15]. Renal injury must be substantial to affect traditional serum biomarkers, with 30% to 50% parenchymal damage required before changes in creatinine can be detected [16]. Drug-induced nephrotoxicity is classified as dose-dependent or dose-independent. In Figure 1 we can identify how renal lesions caused by drugs are classified [17,18].

The main means by which antimicrobials produce nephrotoxicity are by:

a) Acute Tubular Necrosis (Tubuloepithelial Lesion)

b) Acute Interstitial Nephritis (Tubulointerstitial Disease)

c) Crystal Nephropathy (Obstructive)

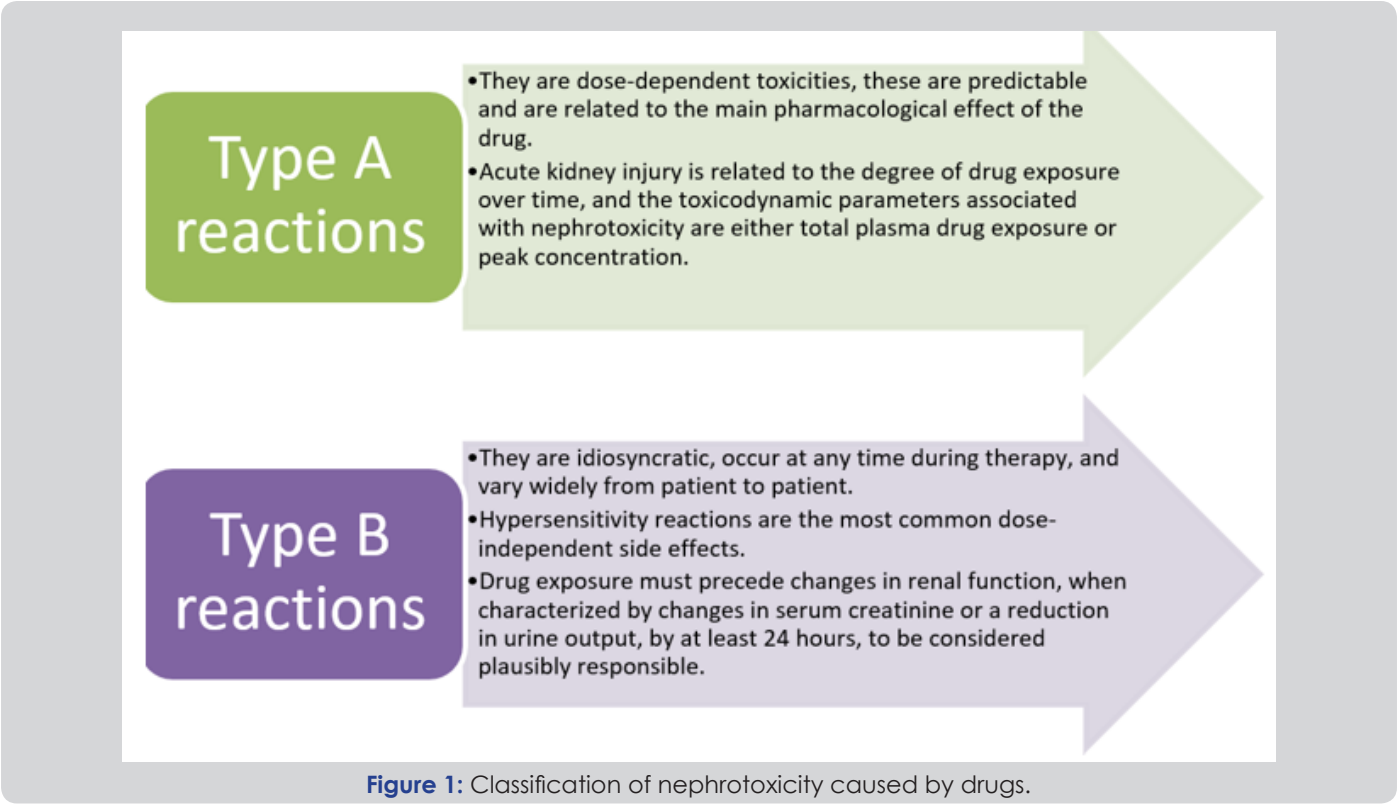

Figure 1: Classification of nephrotoxicity caused by drugs.

Colistin is one of those responsible for the patient developing a type A reaction and a tubuloepithelial lesion [19]. Accumulation of the drug within the epithelial cells of the proximal tubule leads to cell damage, causing increased membrane permeability and cell death, leading to acute tubular necrosis [20,21]. Preclinical data suggest that the use of higher and less frequent doses may minimize toxicity, but experience and data are insufficient to support this strategy in paediatric patients [22].

Tubuloepithelial Lesion

As reported, the cytotoxic effect of the drug is caused by direct contact with the epithelial cells of the proximal or distal tubule. Because this type of toxicity is dose-dependent, it occurs along a spectrum from membrane or organelle damage to complete cell death and necrosis. In Figure 2 we can graphically identify the pathophysiological mechanism of colistin in the induction of nephrotoxicity [23,24].

The mechanism begins with the endocytosis of the drug from the urine into the tubular epithelial cells [1]. Once inside the cell, the drug causes damage to cell organelles [2]. This initiates the process of apoptosis and cell death, and the release of systemic inflammatory signals [3]. Renal blood flow is then reduced [4] as a result of tubuloglomerular feedback mechanisms.

In summary, colistin produces direct cytotoxicity in tubular epithelial cells, most frequently in the proximal tubules. This mechanism is dependent on the dose of colistin and the course of time, the main clinical features are: [25,26].

a) elevated serum creatinine

b) oliguria

c) Increased fractional excretion of sodium

d) microscopic haematuria

e) mild proteinuria

f) hypoalbuminemia

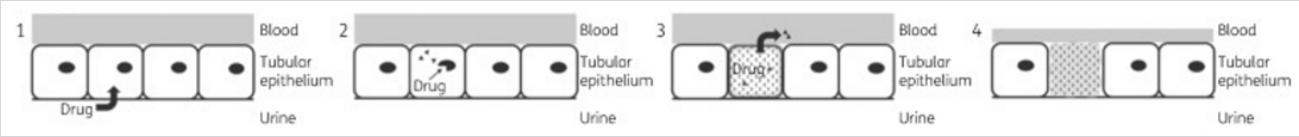

Figure 2: Mechanism of colistin-induced nephrotoxicity.

DISCUSSION

The Intensive Care Unit, in addition to being a specialized and trained site for the care of patients in critical condition, is the main site where invasive procedures are performed, thus increasing hospital-acquired infections as well as mortality. It is estimated that approximately 25% of hospital-acquired infections occur in the intensive care unit. This favours greater bacterial resistance, contributing to the implementation of more effective antimicrobials, but with alarming side effects, such as colistin. The retrospective study carried out by Ayes et al, in which they report patients who received colistin in the adult ICU from January 1 to December 31, 2016, recording age, sex, site of infection among other values, reaching At the conclusion of the patients who received colistin should receive constant and careful monitoring, in order to detect the development of nephrotoxicity as a side effect, since nephrotoxicity occurred in 54.2% of all patients who received colistin [27]. Like the study by Ayes, Bajo and Volkan, in which they carry out a prospective observational study that was carried out among adult patients who received a minimum of 48 hours of intravenous colistin from December 2012 to January 2014 in intensive care units. , concluding that colistin led to a relatively high rate of nephrotoxicity [28]. The nephrotoxic effects caused by colistin is not something new and indisputable, since like the exposed studies there are others that affirm these facts, but it is still necessary to affirm the optimal dose of nephrotoxic effects, since the pharmacokinetics are highly variable in patients in critical condition. A strength of the current study is the methodology implemented, regarding the literature search, and steps in the selection of relevant articles, quality assessment, and data extraction. However, this study has several limitations, which should be taken into account before reaching a conclusion, among these are the little evidence from the analysis of clinical trials that demonstrate the optimal dose of the nephrotoxic effects of colistin, in order to adjust its therapeutic dose without causing nephrotoxicity and resistance to colistin at very low doses, so more studies are needed to answer these questions.

CONCLUSION

Colistin is a cationic polypeptide antibiotic with a cyclic structure that belongs to the group of polymyxins. Due to the number of resistant pathogens, such as carbapenem-resistant Acinetobacter Baumann, Pseudomonas aeruginosa, and Enterobacteriaceae, their implementation is once again increasing in clinical practice. It is believed that 25% of hospital-acquired infections occur in the intensive care unit. The frequency of hospital infections and susceptibility to antibiotics may vary from country to country, from hospital to hospital, and within different units of the same hospital. One of the criteria or scales to quantify colistin nephrotoxicity, which is still being used and implemented in clinical practice, is the risk, injury, failure, loss, and end-stage renal disease (RIFLE) criteria. Risk, Injury, Failure, Loss, ESKD (End Stage Renal Disease). Colistin is one of those responsible for the patient developing a type A reaction and a tubuloepithelial lesion. Colistin produces direct cytotoxicity in tubular epithelial cells, most frequently in the proximal tubules. This mechanism is dependent on the dose of colistin and the course of time, the main clinical features are: elevated serum creatinine, oliguria, increased fractional excretion of sodium, microscopic haematuria, mild proteinuria, hypoalbuminemia.

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