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Nephrotoxic Effect of Aminoglycoside and Polymyxin Antibiotics: A Review

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ABSTRACT
Nephrotoxicity is a significant adverse effect associated with the use of aminoglycoside and polymyxin antibiotics. These antibiotics made its comeback in past few decades in clinical use due to emergence of stubborn gram negative infections and in most of the patient's nephrotoxicity appears in therapeutic courses with these antibiotics. This review critically presents an in-depth analysis of the mechanisms, risk factors, clinical manifestations, prevention, and management strategies for aminoglycoside and polymyxin-induced nephrotoxicity.It was found thatAminoglycoside and polymyxin-induced nephrotoxicity are significant concerns in clinical practice. Understanding the mechanism of nephrotoxicity, risk factor modification, timely identification of clinical manifestations of nephrotoxicity, and implementing supportive measures and pharmacological interventions to treat antimicrobial-induced nephrotoxicity are essential for managing nephrotoxicity and preserving renal function.

Keywords: Nephrotoxicity, aminoglycoside, polymyxin, antibiotic, acute kidney injury.

I. INTRODUCTION:

Antibiotics like aminoglycosides and polymyxin are crucial for treating severe Gram-negative infections. Streptomycin was the first aminoglycoside antibiotic to be utilised for clinical use in the 20th century, and several medications in this family have since followed [1]. Aminoglycoside toxicity has been attributed primarily to tubular damage as a result of selective endocytosis and aggregation of aminoglycoside via multi-ligand receptor megalin. Their cationic structure, which depends on the number of amino groups and on their distribution within the molecule, appears to play a significant role in their toxicity [2]. A family of polypeptide antibiotics known as polymyxins, or Polymyxin A–E, are used to treat bacterial infections. The only polymyxins with therapeutic effects are polymyxin B and polymyxin E, often known as Colistin. Colistinus, a unique species of Bacillus polymyxa, produces it. In the 1970s, Colistin was made available for therapeutic usage. Due to its negative effects, particularly nephrotoxicity, it was nevertheless replaced with less toxic or more acceptable antibiotics roughly ten years after its clinical use. However, the growth of multidrug-resistant Gram-negative bacilli (MDR-GNB), particularly Pseudomonas aeruginosa, Acinetobacter baumannii, and Klebsiella pneumonia, as well as the dearth of new antibiotic development have resulted in the increased usage of Colistin globally in recent years. [3] The most common side effects that limit the use of Colistin are nephrotoxicity and neurotoxicity.Both side effects are cure-dependent and reversible, and permanent kidney or renal damage has infrequently been discerned. Although the exact medium of Colistin-induced nephrotoxicity isn't known, it has been demonstrated that Colistin use is associated with accelerated membrane permeability, oxidative injuries, and latterly, sharp tubular necrosis. Accelerated tubular epithelial cell membrane permeability results in cations, anions, and water affluence, and later cell swelling and lysis. Other mechanisms of nephrotoxicity include oxidative pressure, apoptosis (via mitochondrial, death receptor, and endoplasmic reticulum pathways), cell circle arrest, autophagy, remodelled nitric oxide balance, mitochondrial dysfunction, and oxidative stress or oxidative pressure. But still, their clinical mileage is limited by their implicit ability to produce nephrotoxicity, which can cause acute kidney injury and associated complications. This section provides an overview of aminoglycoside and polymyxin antibiotics' nephrotoxicity and related data.

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II. MECHANISM OF NEPHROTOXICITY

Understanding the mechanism of nephrotoxicity of drugsis essential to understand the type and number of molecules involved in generation of nephrotoxicity in order to develop strategies like megalin ligand targeted prevention techniques to mitigate the nephrotoxicity.Megalin is a huge membrane glycoprotein and an endocytosis receptor that belongs to the low-density lipoprotein receptor gene family. It is abundantly expressed on the luminal surface of renal proximal tubules. There are several different kinds of ligands that bind to megalin, including aminoglycosides, polymyxin, albumin, and cytochrome c. Aminoglycosides and Colistin are considered to accumulate in the renal tubules and harm the kidneys when they bind to the megalin receptor. However, co-administration of competitive agonist ligands of the megalin receptor, such as cytochrome C, would stop aminoglycosides and Colistin drugs from binding to the megalin receptor, reducing their accumulation in renal tubules and attenuating renal damage.

2.1 Mechanisms of aminoglycoside-induced nephrotoxicity

Understanding the mechanisms underlying aminoglycoside-induced nephrotoxicity is crucial for developing strategies to minimise its occurrence.

2.1.1 Renal Uptake:

Aminoglycosides are actively taken up by renal tubular cells through endocytosis. [4] The proximal tubular cells are mainly affected by aminoglycosides. The proximal tubular epithelial cells swiftly take these substances up and integrate them into lysosomes once they contact the phospholipids on the brush border membranes. [5] These substances are readily filtered by the glomeruli. They affect phospholipid metabolism within the tubular cell to provide their primary toxic action. The initial step of nephrotoxicity involves the binding of aminoglycosides to megalin, a receptor on the luminal surface of proximal tubular cells. [6] This interaction triggers internalisation of the drug-receptor complex, leading to the accumulation of aminoglycosides within the renal tubular cells.

2.1.2 Generation of Reactive Oxygen Species (ROS):

Inside renal tubular cells, aminoglycosides undergo intracellular metabolism and generate reactive oxygen species (ROS) as a by-product. [7] The increased production of ROS overwhelms the cellular antioxidant defence systems, leading to oxidative stress. ROS-induced oxidative stress is a critical mediator of aminoglycoside-induced nephrotoxicity, as it contributes to cellular injury and dysfunction.

2.1.3 Mitochondrial Dysfunction:

Aminoglycosides disrupt mitochondrial function within renal tubular cells. [8] They interfere with the electron transport chain, leading to impaired ATP production and mitochondrial membrane depolarization. This disruption compromises cellular energy homeostasis and contributes to the generation of ROS. Additionally, mitochondrial dysfunction triggers apoptotic pathways, further exacerbating renal injury.

2.1.4 Endoplasmic Reticulum Stress:

Aminoglycosides induce endoplasmic reticulum (ER) stress, a condition characterised by the accumulation of unfolded or misfolded proteins within the ER. This ER stress response activates signalling pathways, including the unfolded protein response (UPR), which aims to restore ER homeostasis. [9] Prolonged or severe ER stress can lead to apoptosis and contribute to aminoglycoside-induced nephrotoxicity.

2.1.5 Inflammatory Response:

Aminoglycosides trigger an inflammatory response within the kidneys. They activate nuclear factor kappa B (NF-B), a transcription factor that regulates the expression of pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF-) and interleukin-1 beta (IL-1). [10] The release of these inflammatory mediators attracts immune cells to the site of injury, exacerbating renal inflammation and tissue damage.

2.1.6 Apoptosis:

Apoptosis, a programmed cell death process, plays a significant role in aminoglycoside-induced nephrotoxicity. [11] Aminoglycosides activate both intrinsic and extrinsic apoptotic pathways, leading to the activation of caspases and subsequent cell death. Mitochondrial dysfunction, ER stress, and the generation of ROS contribute to apoptotic signalling cascades.

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2.1.7 Autophagy Dysregulation:

Aminoglycoside exposure can disrupt the normal balance of autophagy, a cellular process responsible for degrading and recycling damaged or unnecessary cellular components. [12] Dysregulation of autophagy can lead to the accumulation of damaged proteins and dysfunctional organelles, exacerbating cellular stress and promoting renal injury.

2.1.8 Summary:

Aminoglycoside-induced nephrotoxicity involves a complex interplay of multiple mechanisms within renal tubular cells.The initial uptake of aminoglycosides, followed by the generation of ROS, mitochondrial dysfunction, ER stress, inflammatory response, apoptosis, and autophagy dysregulation, collectively contribute to renal injury and dysfunction. [13] Future research should focus on developing strategies to mitigate these mechanisms and identify novel therapeutic targets to minimize aminoglycoside-induced nephrotoxicity while maintaining their antibacterial efficacy.

2.2 Mechanisms of Polymyxin-induced Nephrotoxicity

Polymyxins are a class of antibiotics that have experienced a resurgence in clinical use due to the rise of multidrug-resistant gram-negative bacterial infections. However, their utility is limited by the risk of nephrotoxicity, which refers to kidney damage or dysfunction. Understanding the mechanisms underlying polymyxin-induced nephrotoxicity is crucial for optimising their therapeutic use

2.2.1 Interaction with Renal Tubular Cells:

Polymyxins exert their nephrotoxic effects by directly interacting with renal tubular cells. [14] Polymyxin B and Polymyxin E (Colistin) bind to the lipopolysaccharides (LPS) of the outer membrane of gram-negative bacteria, leading to disruption of the bacterial cell wall. However, they can also interact with the lipid components of renal tubular cell membranes, causing membrane destabilisation and cell damage.

2.2.2 Renal Uptake and Accumulation:

Polymyxins are actively taken up by renal tubular cells through endocytosis or passive diffusion. [15] This uptake is mediated by receptors and transporters, including megalin, cubilin, and organic cation transporters (OCTs). Once inside the cells, polymyxins accumulate in the lysosomes, resulting in high intracellular concentrations.

2.2.3 Generation of Reactive Oxygen Species (ROS):

Polymyxin-induced nephrotoxicity involves the production of reactive oxygen species (ROS), such as superoxide anions and hydrogen peroxide. [16] Polymyxin causes mitochondrial dysfunction, leading to electron leakage from the electron transport chain and subsequent ROS generation. The increased production of ROS overwhelms the cellular antioxidant defence systems, leading to oxidative stress and cellular damage.

2.2.4 Disruption of Cellular Membrane Integrity:

Polymyxin can disrupt the integrity of cellular membranes in renal tubular cells. [17] They interact with phospholipids, leading to changes in membrane fluidity and permeability. This disruption can affect cellular functions, including ion transport and membrane-bound enzyme activity, leading to impaired cellular homeostasis and function.

2.2.5 Inflammatory Response:

Polymyxin-induced nephrotoxicity triggers an inflammatory response within the kidneys. The interaction of polymyxin with renal tubular cells leads to the release of pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF-), interleukin-1 beta (IL-1), and interleukin-6 (IL-6). [18] This inflammatory response attracts immune cells to the site of injury, promoting further renal inflammation and tissue damage.

2.2.6 Mitochondrial Dysfunction:

Polymyxin can cause mitochondrial dysfunction in renal tubular cells. They interfere with the electron transport chain, leading to reduced ATP production and disruption of cellular energy metabolism. [19] Additionally, polymyxin induces mitochondrial membrane depolarization and permeabilization, triggering the release of pro-apoptotic factors and contributing to renal cell injury.

2.2.7 Apoptosis and Cell Death:

Apoptosis, a programmed cell death process, is a significant mechanism of polymyxin-induced nephrotoxicity. [20] Polymyxin activates

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apoptotic signalling pathways, including the intrinsic and extrinsic pathways, leading to the activation of caspases and subsequent cell death. Mitochondrial dysfunction, ROS generation, and inflammatory responses contribute to apoptotic cascades and renal cell injury.

2.2.8 Tubular Cell Cytoskeleton Disruption:

Polymyxin can disrupt the cytoskeleton of renal tubular cells, particularly the actin cytoskeleton. [21] This disruption affects cellular morphology, integrity, and function. It can impair cellular adhesion, leading to detachment of tubular cells and disruption of the renal tubular architecture, further exacerbating renal injury.

2.2.9 Impaired Tubular Reabsorption and Secretion:

Polymyxin-induced nephrotoxicity can impair renal tubular reabsorption and secretion processes. [22] The dysfunction of transporters and channels involved in these processes, such as sodium-glucose cotransporters (SGLTs) and organic anion transporters (OATs), can result in altered electrolyte and fluid balance. These disturbances contribute to the development of renal dysfunction and electrolyte imbalances.

2.2.10 Summary:

Polymyxin-induced nephrotoxicity involves a complex interplay of multiple mechanisms within renal tubular cells, including interaction with renal tubular cells, renal uptake and accumulation, generation of ROS, disruption of cellular membrane integrity, inflammatory response, mitochondrial dysfunction, apoptosis and cell death, cytoskeleton disruption, and impaired tubular reabsorption and secretion. Future research should focus on developing strategies to mitigate these mechanisms, such as combination therapy, dosage optimisation, and the development of less nephrotoxic polymyxin analogues, to maximise the therapeutic benefits of polymyxin while minimising renal toxicity.

III. RISK FACTORS:

Several patient- and drug-related factors influence the susceptibility to aminoglycoside and polymyxin-induced nephrotoxicity. [23] This section discusses the impact of factors such as age, pre-existing renal impairment, concomitant nephrotoxic medications, cumulative drug exposure, and genetic predisposition on the development of nephrotoxicity.

3.1 Patient-Related Risk Factors:

Several patient-related factors contribute to the susceptibility to developing nephrotoxicity when receiving aminoglycosides or polymyxin.

3.1.1 Age

Advanced age has been identified as a risk factor for nephrotoxicity induced by these antibiotics. Elderly patients may exhibit altered renal function, decreased drug clearance, and increased vulnerability to drug-induced toxicity. [24]

3.2 Pre-existing Renal Impairment

Patients with pre-existing renal impairment, such as chronic kidney disease or acute kidney injury, are at a higher risk of developing nephrotoxicity when treated with aminoglycosides or polymyxin. [25]

3.3 Concomitant Nephrotoxic Medications

The concurrent use of other nephrotoxic medications, such as nonsteroidal anti-inflammatory drugs, radiocontrast agents, or certain antifungal agents, can potentiate the nephrotoxic effects of aminoglycosides and polymyxin. [26]

3.4 Genetic Predisposition

Genetic factors play a crucial role in individual susceptibility to drug-induced nephrotoxicity. [27] Genetic polymorphisms in drug transporters, drug-metabolising enzymes, and oxidative stress-related genes have been implicated in modifying the risk of nephrotoxicity.

3.5 Drug-Related Risk Factors

Apart from patient-related factors, certain drug-related characteristics influence the risk of aminoglycoside and polymyxin-induced nephrotoxicity. This section discusses the following risk factors:

3.5.1 Dose and Duration of Therapy

The risk of nephrotoxicity is influenced by cumulative drug exposure and the duration of therapy. Prolonged courses of high-dose aminoglycosides or polymyxin are associated with an increased risk of renal damage. [28] Strategies to optimise dosing regimens and minimise cumulative exposure are explored.

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3.5.2 Route of Administration

The route of administration can affect the systemic exposure and renal accumulation of aminoglycosides and polymyxins. Intravenous administration, particularly prolonged infusions, may lead to higher drug concentrations in the kidneys, increasing the risk of nephrotoxicity. [29] The impact of different administration routes and infusion strategies is discussed.

3.5.3 Combination Therapy

Combining aminoglycosides or polymyxin with other nephrotoxic medications, such as vancomycin or loop diuretics, can potentiate the nephrotoxic effects. [30]

IV. PREVENTION OF AMINOGLYCOSIDE AND POLYMYXIN-INDUCED NEPHROTOXICITY

4.1 Risk Factor Modification:

Several risk factors contribute to the development of aminoglycoside- and polymyxin-induced nephrotoxicity. Strategies for modifying modifiable risk factors includes optimising dosing regimens, avoiding concomitant nephrotoxic medications, and maintaining adequate hydration. It also emphasises the importance of patient-specific factors, such as age, comorbidities, and renal function, in guiding treatment decisions. [31]

4.2 Optimisation of Dosing Regimens:

Appropriate dosing regimens are essential to minimise the risk of nephrotoxicity. [32]Strategies for optimising aminoglycoside and polymyxin dosing includes individualised dosing based on patient characteristics, therapeutic drug monitoring, and adjustment of dose and frequency to maintain therapeutic efficacy while minimising renal toxicity. It also explores the pharmacokinetic and pharmacodynamic principles underlying dosing optimisation.

4.3 Combination Therapy

Considerations Combining aminoglycosides or polymyxin with other nephrotoxic agents can potentiate the risk of nephrotoxicity. [33]Concomitant use of other medications, such as vancomycin or Non-steroidal anti-inflammatory drugs like aspirin along with aminoglycosides or polymyxin antibiotics increases risk of nephrotoxicity.

4.4 Renal Function Monitoring

Regular monitoring of renal functionsuch as estimation of serum creatinine, estimated glomerular filtration rate (eGFR), and urine output is essential for the early detection of nephrotoxicity and intervention It highlights the need for close monitoring in patients with pre-existing renal impairment or those at higher risk of nephrotoxicity. [34]

4.5 Hydration and Volume Status Optimisation

Maintaining adequate hydration and optimising volume status can help prevent aminoglycoside and polymyxin-induced nephrotoxicity. [35] This emphasises the importance of ensuring proper hydration before and during therapy, particularly in high-risk patients, and discusses the potential mechanisms by which hydration may mitigate renal toxicity.

4.6 Genetic Screening and Personalised Medicine

Genetic variations can influence an individual's susceptibility to nephrotoxicity. [36] This reveals the potential role of genetic screening in identifying patients at higher risk and enabling personalised medicine approaches. It highlights the importance of pharmacogenetic testing to guide drug selection and dosing strategies. The ethical considerations and practical implications of genetic screening are also should be considered.

4.8 Education and Awareness:

Promoting education and awareness among healthcare professionals regarding the risk of nephrotoxicity and the appropriate preventive measures is crucial. This emphasises the significance of educating clinicians about the potential nephrotoxic effects of aminoglycosides and polymyxins, risk factors, monitoring guidelines, and preventive strategies [37]. Educational initiatives, clinical guidelines, and the integration of preventive measures should be introduced into clinical practise.

4.9 Summary:

Preventing aminoglycoside and polymyxin-induced nephrotoxicity requires a multifaceted approach, including optimising dosing regimens, monitoring renal function, maintaining hydration, considering nephroprotective agents, and implementing personalised medicine strategies. By incorporating these preventive measures, clinicians

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can reduce the incidence and severity of nephrotoxicity and improve patient outcomes.

V. MANAGEMENT:

The effective management of aminoglycoside and polymyxin-induced nephrotoxicity relies on early recognition and appropriate interventions. Understanding and implementing these strategies are crucial for mitigating renal damage and optimising patient outcomes.

5.1 Recognition and Early Detection:

The timely recognition and early detection of nephrotoxicity are vital for initiating appropriate management. [38] Clinical manifestations and laboratory parameters are used to diagnose aminoglycoside and polymyxin-induced nephrotoxicity. It highlights the importance of vigilant monitoring, including renal function tests and urine output assessments, to promptly identify renal toxicity.

5.2 Supportive Measures:

Supportive measuressuch as optimising fluid balance, electrolyte management, hemodynamic support, renal replacement therapy including intermittent haemolysis and continuous renal replacement therapy, in severe cases play a crucial role in the management of aminoglycoside and polymyxin-induced nephrotoxicity. of requiring renal support.

5.3 Pharmacological Interventions:

Reno protective agents have been investigated for their potential to reduce aminoglycoside and polymyxin-induced nephrotoxicity. Various Reno-protective agents used in management of nephrotoxicity are enlisted below:

1.Diuretics (furosemide)
2.Antioxidants (vitamin E, vitamin C, alpha-lipoic acid,)
3.N-acetyl cysteine (amino acid)
4.Sodium bicarbonate (alkalinising agent)
5.Resveratrol (antioxidant/anti-inflammatory/cytoprotective)
6.Cytochrome C (megalin ligand)
7.Erythropoietin (Renal hormone)
8.SGLT2 (sodium glucose cotransporter-2)
9.Atrasentan (blocks effect of endothelin-1)
10.Spherical carbon adsorbent (of uremic toxins)
11.Bardoxolone methyl (Oleanane triterpenoid-antioxidant/anti-inflammatory/cytoprotective)
12.Statins (atorvastatin, rosuvastatin)
13. Mannitol (osmotic diuretic)
14.Magnesium (renal calculi inhibition and counteract phosphate toxicity)
15.Natriuretic Peptides (Ularitide, Vosoritide)
16.Prostaglandins -PGE2 Prostacyclin
17. Cilastatin (dehydropeptidaseinhibitor)
18.Nitric oxide synthase inhibitors (L-citrulline, agmatine, NG-Dimethyl-L-arginine)
19.Catecholamine's(Adrenaline, Noradrenaline, Dopamine, Dobutamine, Dopexamine)
20.Bradykinin (peptide vasodilator)

VI. CONCLUSION

Aminoglycosides and polymyxin are potent antibiotics used in the treatment of severe gram-negative infections. However, their use is associated with the risk of nephrotoxicity. Throughout this comprehensive review, exploration of various aspects of aminoglycoside and polymyxin-induced nephrotoxicity, including its mechanism of nephrotoxicity, risk factors, prevention, and pharmacological management strategies, was done. Understanding the mechanisms underlying aminoglycoside-induced nephrotoxicity is crucial for developing strategies to minimise its occurrence. Supportive measures play a critical role in managing aminoglycoside and polymyxin-induced nephrotoxicity. In severe cases requiring renal support, renal replacement therapy, such as intermittent haemolysis or continuous renal replacement therapy, may be necessary. Pharmacological interventions have been explored to attenuate aminoglycoside and polymyxin-induced nephrotoxicity. Reno protective agents, such as antioxidants, N-acetyl cysteine, and sodium bicarbonate, have shown potential in reducing oxidative stress, inflammation, and cellular apoptosis associated with nephrotoxicity. [39] However, the clinical evidence supporting their use is limited, and further research is needed to establish their efficacy and optimal dosing regimens.

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