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A COMPREHENSIVE REVIEW ON DRUG-INDUCED (AMINOGLYOSIDES) ACUTE KIDNEY INJURY: MECHANISMS, RISK FACTORS, DIAGNOSIS, AND THERAPEUTIC APPROACHES

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ABSTRACT

Aminoglycosides are known to be potent bactericidal antibiotics that are widely used for severe gram-negative infections; however, the use of these drugs is limited simultaneously due to their nephrotoxicity leading to acute kidney injury (AKI). This review provides a detailed overview of aminoglycoside-induced AKI, focusing on its mechanisms, risk factors, clinical diagnosis, and management. The pathophysiology involves accumulation of the drug in proximal tubular cells with associated oxidative stress, mitochondrial injury, and apoptosis. Risk factors include high cumulative doses, prolonged duration of therapy, pre-existing renal disease, and use of concomitant nephrotoxic agents. Clinical diagnosis has evolved from the traditional serum creatinine towards newer biomarker candidates like NGAL and KIM-1. Treatment usually involves immediate discontinuation of the offending agent, renal supportive care, therapeutic drug monitoring, and potentially, novel agents with renoprotective properties. Despite recent advances, significant gaps in the early recognition and prevention of toxicity remain. The future holds promise for individualized dosing regimens, biomarker-guided therapy, and safer drug formulations to maintain antimicrobial activity while ensuring renal safety.

KEYWORDS: Aminoglycosides, Acute Kidney Injury, Nephrotoxicity, Oxidative Stress, Therapeutic Drug Monitoring, Renal Protection, Biomarkers.

INTRODUCTION

Aminoglycosides are a class of bactericidal antibiotics mostly indicated in severe gram-negative bacterial infections. Some of the most commonly used agents are gentamicin, tobramycin, amikacin, and streptomycin. They bind irreversibly to the 30S subunit of bacterial ribosomes thereby inhibiting protein synthesis, which culminates in bacterial cell death. Owing to the rapid kill and synergy with β-lactam antibiotics, aminoglycosides are often used in life-threatening sepsis, hospital-acquired pneumonia, and urinary tract infections. Despite their impressive killing ability, their use in the clinic is limited by a narrow therapeutic index combined with serious nephrotoxicity and ototoxicity, requiring careful consideration in dosing and monitoring.[1,2]

Since their introduction in the 1940s, aminoglycosides have played important roles in treating infectious diseases, especially in the pre-antibiotic and early post-antibiotic eras. Streptomycin was the first aminoglycoside discovered and the landmark drug in the treatment of tuberculosis. Over the years, newer aminoglycosides like gentamicin and amikacin were developed to widen their antibacterial spectrum and reduce resistance. Subsequently, they became essential therapeutic modalities in the ICU for the management of multidrug-resistant organisms. Yet they lay on the fence as far as their potential to cause AKI and hearing loss have been greatly fronted in recent decades, generally with the availability of safer antibiotic alternatives.[3,4]

An aminoglycosides-induced AKI is a matter of concern for the clinicians because of its dose-dependent toxicity with an element of irreversibility. Despite its newfound competition from newer antibiotics, aminoglycosides still have their place in the treatment of resistant infections, especially in resource-limited settings. A proper appreciation of the mechanisms of nephrotoxicity is critical to warding off kidney injury and paving the way for better patient outcomes. This review intends to furnish a central insight into the pathophysiology, risk factors, diagnosis, and management of aminoglycoside-induced AKI. The article sets forth advances in biomarker research and nephroprotective strategies associated with aminoglycoside therapy, aiming to help clinicians find an appropriate equilibrium between adequate treatment and renal safety in at-risk populations.[5,6]

Aminoglycoside-mediated nephrotoxicity is another major cause of drug-induced acute kidney injury (AKI), especially amongst hospitalized and critically ill patients. Literature suggests some degree of renal impairment in 10-25% of patients treated with aminoglycosides. The risk is higher in lower income settings, where therapeutic drug monitoring is usually unavailable. In high-burden settings such as neonatal intensive care units, aminoglycoside-related AKI may translate into increased hospital stay, healthcare costs, and mortality. The fulminant nature of AKI has indeed spread its consequences worldwide, with progressive development into chronic kidney disease (CKD), thereby demanding more awareness, monitoring protocols, and evidence-based prevention strategies.[7,8]

OVERVIEW OF AMINOGLYCOSIDES

Aminoglycosides are a group of broad-spectrum antibiotics whose origin lies in Streptomyces and Micromonospora species. They are mainly administered to treat serious infections caused by aerobic gram-negative bacilli such as Pseudomonas aeruginosa, Klebsiella, Enterobacter, and Escherichia coli. Aminoglycosides exhibit bactericidal action by binding the 30S ribosomal units of the bacteria, preventing protein synthesis, and causing misreading of the mRNA. Their pharmacodynamics features include a fast onset of action, post-antibiotic effect, and concentration-dependent killing, which makes them suitable applications in critical care and surgical prophylaxis.

Nevertheless, aminoglycosides become even more limited, given their ototoxic and nephrotoxic natures, especially to patients with pre-existing renal dysfunction. Usually, TDM must accompany their administration to curb toxicity and maximize efficacy. They are usually given in combination with beta-lactam antibiotics for synergistic effects, mainly in the management of endocarditis, sepsis, and febrile neutropenia.[9]

HISTORICAL BACKGROUND

The discovery of aminoglycosides was perhaps one of the most important turning points in the history of antimicrobial chemotherapy. In 1943, the first of the aminoglycosides, streptomycin, was discovered by Selman Waksman and his team from Streptomyces griseus. Streptomycin became the very first antibiotic that could effectively treat TB, representing a key step in the process that changed tuberculosis from a fatal disease into a treatable infection.

Subsequently, following streptomycin, neomycin came into the market in 1949, and in the 1950s came kanamycin, thus expanding the scope of aminoglycoside therapy. In the 1960s and 70s, the next wave arrived with gentamicin, tobramycin, and amikacin, each carrying forth improvements in the spectrum of activity and resistance profile. These agents had become the mainstays of treatment for nosocomial infections and were of considerable value prior to the availability of a newer generation of antibiotics.

With the increase over the decades in multidrug-resistant (MDR) pathogens, there has been a resurgence of interest for the aminoglycosides, especially amikacin, owing to its resistance to many aminoglycoside-modifying enzymes. With such potential toxicities, however, aminoglycosides continue to remain a crucial component of the antibiotic armamentarium, especially in resource-limited settings.[10,11]

Examples of Aminoglycosides[12]

Drug Name	Source	Spectrum of Activity
Gentamicin	Micromonospora purpurea	Broad (esp. gram-negative)
Tobramycin	Streptomyces tenebrarius	Stronger against Pseudomonas spp.
Amikacin	Semi-synthetic from kanamycin A	Broad, including resistant gram-negatives
Streptomycin	Streptomyces griseus	Active against Mycobacterium

		tuberculosis
Neomycin	Streptomyces fradiae	Broad, but toxic systemically

MECHANISM OF ACTION

The mechanism of bactericidal action of aminoglycosides involves the irreversible binding to the 30S subunit of the bacterial ribosome and interfering with the bacterial process of translating mRNA into proteins. When the drug binds to the ribosome, it causes a misreading of the mRNA codon resulting in the formation of abnormal or nonfunctional proteins. These abnormal proteins then interfere with bacterial cell viability. Unlike most other protein synthesis inhibitors, aminoglycosides are bactericidal, not bacteriostatic. The uptake into bacterial cells by the oxygen-dependent, energy-driven transport system is what renders aminoglycosides ineffective against anaerobes. Once within the cell, they bind to the initiation complex of 30S ribosomal subunit and disrupt protein synthesis by promoting insertion of incorrect amino acids, hence leading to production of faulty peptides and damage to bacterial membranes. This process causes not only damage to protein function but also elevation of membrane permeability so that more aminoglycoside molecules can enter, thus facilitating further killing of bacteria. Killing is concentration-dependent in nature, and they demonstrate a post-antibiotic effect, wherein the suppression of bacteria persists even when plasma drug levels have fallen below the minimum inhibitory concentration (MIC).[13,14]

PHARMACOKINETICS OF AMINOGYCOSIDES

Parameter	Details
Absorption	- Oral bioavailability: <1% (negligible; requires IV/IM route for systemic effect) - Peak serum concentration (Cmax): 5–10 µg/mL (gentamicin, after 1–2 mg/kg IV dose)
Distribution	- Volume of distribution (Vd): ~0.2–0.3 L/kg (extracellular fluid) - Poor penetration into CSF (approx. 10% of serum levels with inflamed meninges) - High concentrations in renal cortex and inner ear (toxicity sites)
Protein Binding	<10% (low plasma protein binding, mostly free drug available for activity and toxicity)
Metabolism	- Not metabolized; pharmacologically unchanged in the body
Excretion	- Route: Renal excretion via glomerular filtration - Clearance: ~0.8–1.5 mL/min/kg (proportional to GFR) - Elimination half-life: 2–3 hours (normal renal function); up to 20–60 hours in end-stage renal disease - 90–100% of the dose excreted unchanged in urine within 24 hours
Therapeutic Drug Monitoring (TDM)	- Peak (gentamicin): 5–10 µg/mL - Trough (gentamicin): <2 µg/mL - Amikacin peak: 20–30 µg/mL; trough: <5–10 µg/mL[15,16]

THERAPEUTIC INDICATIONS AND COMMON DOSAGE REGIMENS

Aminoglycosides are typically employed for **serious gram-negative bacterial infections**, particularly in hospital and ICU settings. They are often used **in combination with beta-lactam antibiotics or glycopeptides** to broaden antibacterial coverage and enhance efficacy.

- **Gentamicin**: 3–5 mg/kg/day IV/IM in divided doses every 8 hours (traditional) or 5–7 mg/kg once daily (extended-interval dosing).
- **Tobramycin**: 5–7 mg/kg once daily IV for susceptible infections; also available in inhalational form for cystic fibrosis.
- **Amikacin**: 15–20 mg/kg/day IV, either once daily or divided into two doses.
- **Streptomycin**: 15 mg/kg/day IM in TB treatment.
- **Neomycin**: Topical application; oral use limited to gut decontamination due to systemic toxicity.

Therapeutic drug monitoring (TDM) is essential to optimize efficacy and prevent toxicity. **Peak and trough plasma levels** are routinely measured, especially during prolonged therapy or in patients with renal impairment.[17,18]

ACUTE KIDNEY INJURY (AKI)

An abrupt impairment in renal functions resulting in the accumulation of nitrogenous wastes, disturbance of electrolytes, and fluid imbalance has been termed as Acute Kidney Injury (AKI). The timeline of AKI ranges from a matter of hours to days, depending upon which it can be a benign transient increase in serum creatinine or a catastrophic renal failure requiring dialysis. It is associated with an increased risk of morbidity with mortality and cost, especially in critically ill hospitalized patients. Therefore, early detection, staging, and prompt management of AKI are necessary to prevent the end-stage renal disease.[19]

PATHOPHYSIOLOGY AND MECHANISMS OF AMINOGLYCOSIDE-INDUCED ACUTE KIDNEY INJURY (AKI)

1. Renal Accumulation and Proximal Tubule Uptake

Aminoglycosides are water-soluble, polycationic antibiotics that manage to get filtered through the glomerulus and accumulate preferentially in kidney

proximal tubules, especially the S1 and S2 segments. Their reabsorption takes place mainly through endocytic receptors such as megalin and cubilin, facilitating the endocytosis of these drugs into tubular epithelial cells through clathrin-coated pits. Following internalization, aminoglycosides tend to accumulate in specific intracellular organelles, namely lysosomes, that contain anionic phospholipid substrates. Progressive accumulation of aminoglycosides in renal tissue, dependent on dose and time, is an important early stage in the pathogenesis of nephrotoxicity. This mechanism, in addition to raising intrarenal aminoglycoside concentrations, renders proximal tubules more susceptible to toxic insult.[20]

2. Lysosomal Dysfunction and Phospholipidosis

In the proximal tubular cells, aminoglycosides bind strongly to acidic phospholipids located at lysosomal membranes, thereby inhibiting lysosomal enzymes, such as phospholipases. Plasma membrane changes lead to abnormal phospholipid accumulation, a phenomenon known as phospholipidosis, hence disrupting lysosomal functioning. These overburdening lysosomes expand and become fragile-- ultimately rupturing. Lysosomes in turn put cathepsins and other hydrolytic enzymes into the cytoplasm, which results in destroying cell parts through autodigestion. This destroys the cell, starting tubular cell injury--an early but irreversible stage of AKI.[21]

3. Mitochondrial Dysfunction and Oxidative Stress

Aminoglycosides localize within mitochondria and obstruct mitochondrial respiration and consequently ATP synthesis, culminating in bioenergetic failure. Extremely disturbed in the electron transport chain, it promotes the excess generation of reactive oxygen species (ROS), mainly superoxide anions and hydrogen peroxide. ROS attack cell membranes through lipid peroxidation, modify proteins by oxidation, and damage DNA, thereby propagating cellular damage further. Such oxidative stress surpasses the cell's antioxidant mechanisms (like glutathione and superoxide dismutase), propelling mitochondrial swelling and opening of the permeability transition pore until the cells die through apoptotic and necrotic routes.[22]

4. Apoptosis and Necrosis of Tubular Epithelial Cells

Aminoglycosides continue to activate numerous cell death pathways as oxidative damage progresses, primarily apoptosis and necrosis, depending upon the degree and extent of injury. Such apoptotic events are executed via the mitochondrial (intrinsic) and death receptor (extrinsic) pathways. In the mitochondrial pathway, cytochrome c release and activation of caspase-9 and caspase-3 occur, along with a change in the Bax/Bcl-2 ratio toward a pro-apoptotic one. In contrast, severe energy depletion leads to necrosis, where cell swelling occurs with membrane rupture and loss of intracellular contents into the tubular lumen. Necrotic debris and sloughed epithelial cells may coalesce into proteinaceous casts, obstructing the tubules and thereby limiting glomerular filtration further.[23]

5. Inflammatory and Immune-Mediated Injury

In response to injury, tubular epithelial cells release pro-inflammatory cytokines and chemokines such as TNF-α, IL-6, IL-8, and MCP-1 that attract neutrophils and macrophages to the injury locus. This immune reaction causes tubulointerstitial inflammation that propagates tissue damage. There may be TLR activation on tubular cells by aminoglycosides further releasing cytokines and promoting inflammation. Upregulation of adhesion molecules, including ICAM-1, on renal endothelial and epithelial cells shows greater adhesion and transendothelial migration abilities for leukocytes, thereby promoting renal injury.[24]

6. Altered Renal Hemodynamics

On one hand, aminoglycosides induced vasoconstriction of the afferent arterioles affecting renal blood flow. This vasoconstriction was possibly caused by increased endothelin-type activity and reduced NO-type activity. Hence, these changes decrease renal perfusion pressure and alter glomerular filtration rate (GFR). On the other hand, tubular injury and cast formation predispose to tubular backleak, thereby increasing intratubular pressure and impairing GFR. Such hemodynamic changes provide the functional component of AKI, which worsens the tubular injury caused by direct cellular toxicity.[25]

7. Impaired Regeneration and Chronic Progression

Under normal circumstances, injured tubular epithelial cells go through the repair processes by the alterations of dedifferentiation, proliferation, and redifferentiation. Repeated and severe exposure to aminoglycosides, however, sets a hindrance to regeneration. When the injury becomes persistent, there is tubulointerstitial fibrosis, which involves myofibroblast activation, extracellular matrix deposition, and peritubular capillary loss. Eventually, this leads to irreversible chronic kidney disease (CKD). Moreover, the processes of maladaptive repair, including epithelial-to-mesenchymal transition (EMT), also drive the fibrotic transformation of renal tissue.[26]

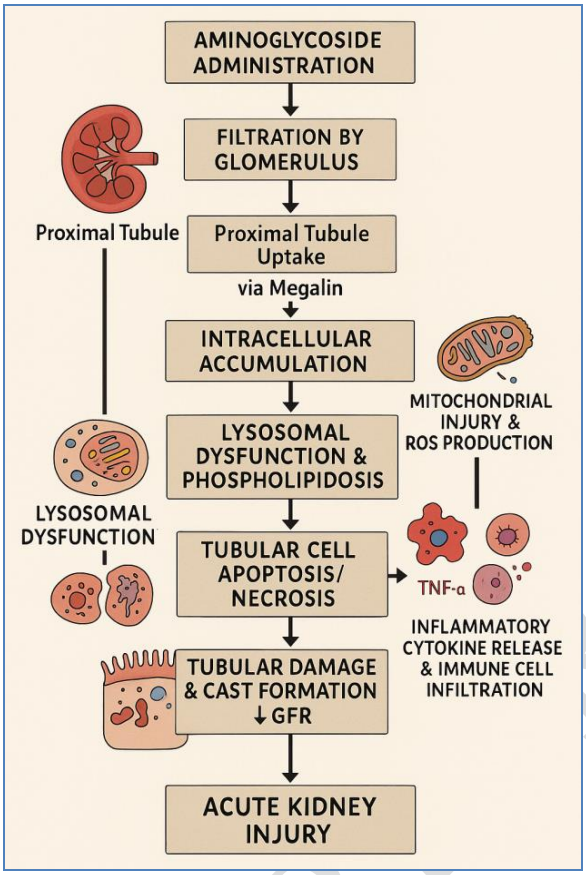

Figure 1: Mechanisms of Aminoglycoside-Induced Acute Kidney Injury (AKI).

RISK FACTORS

Category	Risk Factor	Description/Explanation
Patient-Related	Age > 60 years	Decreased renal reserve and impaired drug clearance in elderly.
	Pre-existing renal impairment	Lower baseline GFR increases susceptibility to further nephrotoxic injury.
	Volume depletion	Hypovolemia reduces renal perfusion, enhancing tubular damage.
	Sepsis or critical illness	Associated with hypotension, inflammation, and multi-organ stress.
	Hypoalbuminemia	Leads to higher free (active) drug concentration.
	Genetic predisposition	Variants in megalin/cubilin genes may increase tubular uptake.
Drug-Related	High cumulative dose of aminoglycoside	Increased exposure correlates with higher renal accumulation.[27]
	Prolonged duration of therapy (>5–7 days)	Risk increases with duration due to sustained tubular accumulation.
	High peak or trough serum levels	Trough levels >2 mg/L (gentamicin/tobramycin) or >10 mg/L (amikacin) raise AKI risk.
	Once-daily dosing (protective)	Less nephrotoxic than multiple daily dosing due to lower sustained intracellular levels.
Concomitant Medications	Use of other nephrotoxic drugs	E.g., vancomycin, amphotericin B, NSAIDs, contrast agents — additive nephrotoxicity.
	Diuretics (e.g., furosemide)	May lead to dehydration and electrolyte imbalance.
Procedure-Related	Major surgery (especially cardiac or abdominal)	Hypoperfusion and use of nephrotoxic agents during surgery contribute to risk.
	Radiocontrast exposure	Synergistic nephrotoxicity when used with aminoglycosides.
Monitoring-Related	Inadequate therapeutic drug monitoring (TDM)	Failure to adjust dosing based on serum levels increases toxicity risk.
	Delayed recognition of early renal dysfunction	Lack of routine creatinine/GFR monitoring can lead to unrecognized injury progression.[28]

CLINICAL SYMPTOMS AND DIAGNOSIS

	Parameter	Description
Clinical Symptoms	Fatigue, weakness	Due to accumulation of nitrogenous waste (uremia)
	Decreased urine output (oliguria)	May occur but often AKI is non-oliguric in aminoglycoside toxicity
	Nausea, vomiting, anorexia	Resulting from azotemia
	Peripheral edema	Due to fluid retention and reduced GFR
	Hypertension	Fluid overload or secondary activation of RAAS
Laboratory Findings	Serum Creatinine	Gradual rise over 5–10 days after exposure
	Blood Urea Nitrogen (BUN)	Elevated due to impaired nitrogen excretion
	Estimated GFR	Decreased eGFR reflects worsening kidney function
	Serum Electrolytes	Hypomagnesemia, hypokalemia, hyponatremia due to tubular dysfunction
Urinalysis	Proteinuria	Typically low to moderate range
	Casts	Granular (muddy brown) casts suggest tubular injury
	Cells	Renal tubular epithelial cells may be present
Biomarkers (Early AKI)	NGAL (Neutrophil Gelatinase-Associated Lipocalin)	Rises earlier than creatinine, marker of tubular damage
	KIM-1 (Kidney Injury Molecule-1)	Elevated in proximal tubule injury
	Cystatin C	More reliable than creatinine for early detection
Imaging	Renal Ultrasound	Often normal; used to exclude obstruction or other structural causes
Other Diagnostic Tools	Therapeutic Drug Monitoring (TDM)	Monitoring peak/trough levels of aminoglycosides to adjust dosage
	Renal Biopsy (rarely)	Considered only in unclear or severe cases for definitive diagnosis.[29,30]

MANAGEMENT AND THERAPEUTIC APPROACHES

The onset and progression of acute aminoglycoside kidney injury demand prompt and personalized interventions so as to curtail the extent of kidney damage and improve patient outcomes. Management broadly encompasses discontinuing or modifying treatment, providing supportive care, and giving specific intervention.

Discontinuation or Substitution of the Offending Drug

The instrumental and immediate step upon recognition or a mere suspicion of aminoglycoside-associated nephrotoxicity is the discontinuation of the offending agent. If aminoglycosides cannot be avoided owing to nonavailability of alternatives (in multidrug-resistant infections, for instance), dose reduction in accordance with renal function and TDM should be contemplated. Wherever possible, the clinician must consider replacing these agents with others that are less nephrotoxic (e.g., beta-lactams, linezolid, or fosfomycin).[31]

Supportive Therapy

Supportive care remains the **mainstay** of managing AG-AKI. It includes:

- **Fluid and Electrolyte Management**: Preserving euvolemia and preventing any volume depletion will hence lead to less aggravation of renal perfusion. Careful administration of fluid must be given attention so as to avoid fluid overload.
- **Electrolyte Monitoring and Correction**: Hypomagnesemia, hypokalemia, and metabolic acidosis being common entities in AG-AKI have to be corrected.
- **Blood Pressure Control**: Hypotension must be avoided to preserve renal perfusion.
- **Avoidance of Other Nephrotoxins**: Concomitant use of NSAIDs, radiocontrast agents, and other nephrotoxic antibiotics (e.g., vancomycin) should be either avoided or minimized.

In severe cases, renal replacement therapy (RRT) including intermittent hemodialysis, or CRRT may be required, especially in oliguric or anuric patients with fluid overload, electrolyte imbalances, or uremic complications.[32]

Pharmacological and Adjunctive Interventions

Several pharmacological agents have been studied for their potential to prevent or mitigate aminoglycoside nephrotoxicity, though their routine use is not yet standardized:

- **N-Acetylcysteine (NAC)**: As an antioxidant, NAC may reduce oxidative stress-mediated tubular injury. Clinical evidence is mixed, and more trials are needed.
- **Ascorbic Acid (Vitamin C)** and **Vitamin E**: These have shown renal protective effects in some experimental studies by reducing free radical damage.
- **Melatonin and Coenzyme Q10**: Investigational agents with antioxidant and mitochondrial stabilizing effects have shown promise in preclinical models.
- **Sodium 2-mercaptoethane Sulfonate (MESNA)**: Acts as a free radical scavenger; animal models suggest nephroprotection, though clinical data are sparse.
- **Statins**: Possess pleiotropic anti-inflammatory and antioxidative effects, potentially reducing tubular apoptosis.[33]

Novel and Emerging Therapies

Further research is ongoing in the design of aminoglycoside analogs with reduced nephrotoxicity, such as plazomicin. Drug delivery systems are under study that entrap the drug at the infection site while sparing renal tissues (e.g., liposomal formulations or conjugates). The views on gene therapy, renal protective peptides, and cell-based therapies (such as mesenchymal stem cells) are being explored in experimental settings. These may someday provide new treatments for nephropathy prevention and repair.[34]

PROGNOSIS AND OUTCOMES

Depending on the severity of renal impairment, timeliness of diagnosis, and whether intervention is promptly undertaken, the prognosis of aminoglycoside-induced acute kidney injury may vary. In almost all cases, renal function will recover within days to weeks if the nephrotoxic insult is recognized early and aminoglycosides are stopped in time. However, patients with prior kidney disease, the elderly, and prolonged exposure to aminoglycosides are at high risk for incomplete recovery and progression into chronic kidney disease (CKD). Up to 10-15% of patients having drug-induced AKI may develop permanent renal dysfunction, suggest statistics. Furthermore, aminoglycoside-induced nephrotoxicity contributes to prolonged hospitalization, need for renal replacement therapy, and costs to the healthcare system. In critically ill populations, aminoglycoside-related AKI is also associated with increased morbidity and mortality, especially if complicated by sepsis, hypotension, or multi-organ dysfunction. Hence, prevention, timely diagnosis, and individualization of aminoglycoside dosing remain crucial for improving long-term patient outcomes.[35,36]

RESEARCH GAPS AND FUTURE DIRECTIONS

Despite decades of clinical use, major gaps persist in our understanding of aminoglycoside-induced nephrotoxicity. The principal limitation has been the absence of reliable early biomarkers to predict AKI before overt changes of serum creatinine are observed. Biomarkers such as NGAL, KIM-1, and cystatin C have been investigated with promising results, but their utility still awaits clinical standardization. Furthermore, much of the data we have come from animal models or observational studies, and there are very few large, randomized controlled trials for prevention and treatment. In particular, antioxidant therapies and novel drug formulations (e.g., liposomal or nanoparticle-bound aminoglycosides) and gene-targeted therapies are still far from being studied clinically. We need more clinical decision support tools and artificial intelligence-based algorithms to optimize dosing in high-risk patients. A focus should be put into future research on personalized medicine approaches, integrating pharmacogenomics, panels of renal biomarkers, and real-time therapeutic drug monitoring to mitigate toxicity without diminishing antimicrobial efficacy. The approach will require collaborative and interdisciplinary work.[37,38]

CONCLUSION

Aminoglycoside-induced acute kidney injury (AKI) continues to pose a significant challenge in clinical practice, particularly among hospital and ICU patients. While these antibiotics will continue to be used in treating serious gram-negative infections, their potential for nephrotoxicity should always be taken into consideration. When the complex mechanisms of toxicity are understood, from tubular accumulation at the proximal level to oxidative stress and apoptosis, then one can think of ways to reduce its occurrence. The best way to reduce damage includes prompt diagnosis, appropriate dosing according to renal function, and drug monitoring. Subsequent implementation of antioxidant therapies and these emerging new biomarkers might yield more advancements, but more clinical studies are warranted. An integrative patient-centered approach then would guarantee the best therapeutic outcome with the least harm to the kidneys.

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