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Review Article

Animals Models on Drug Induced Renal Injury

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ABSTRACT

The kidneys are exceptionally susceptible to drug-induced injury due to their high blood flow and the concentration of drugs during filtration and excretion. This condition, known as drug-induced renal injury (DIRI), is a significant contributor to acute kidney injury and can lead to chronic kidney disease. A range of common therapeutic agents, including aminoglycosides, cisplatin, non-steroidal anti-inflammatory drugs (NSAIDs), and calcineurin inhibitors, are recognized for their nephrotoxic potential. The resulting damage can affect various renal structures, such as the tubules, interstitium, glomeruli, or vasculature, with severity ranging from subtle, subclinical changes to severe dysfunction. Preclinical research utilizes models like rodents, zebrafish, and rabbits to explore DIRI mechanisms and screen for protective compounds. Key pathogenic pathways involve oxidative stress, inflammation, apoptosis, and mitochondrial damage. Despite these efforts, translating findings to clinical practice is challenging due to interspecies differences and inconsistent experimental designs. A major hurdle in managing DIRI is the delayed detection with traditional biomarkers like serum creatinine and BUN, which only rise after significant injury has occurred. Consequently, more sensitive and early indicators are being investigated. These novel biomarkers, such as Kidney Injury Molecule-1 (KIM-1), Neutrophil Gelatinase-Associated Lipocalin (NGAL), and inflammatory cytokines like IL-18 and TNF-alpha, offer the potential for earlier diagnosis. To improve clinical translation, future research must focus on standardizing study protocols, validating these new biomarkers, and employing advanced models like kidney organoids and microfluidic chips, which better replicate human kidney physiology.

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INTRODUCTION

Critical to homeostasis, the kidneys are multitaskers: they produce and release key hormones like renin and erythropoietin, clear metabolic waste from the bloodstream, and keep a tight rein on electrolytes, pH levels, and overall fluid balance. To pull this off, they filter roughly a quarter of the heart's resting output every single minute. Yet, this very efficiency comes with a catch-the sheer volume of substances they process and reabsorb leaves them highly exposed to harmful compounds, making them particularly prone to toxic damage. Given this vulnerability, it's no surprise that a number of medications can lead to Drug-Induced Renal Injury (DIRI). In fact, DIRI is a factor in about 20% of all nephrotoxicity cases and most often shows up as impaired function in the kidney's tubules[1].

Epidemiology

CKD prevalence has climbed sharply worldwide, more than doubling from 378 million adults in 1990 to 788 million in 2023 - a shift only partly explained by population growth, since the age-standardised rate also rose to 14.2%. Regional burden is uneven: North Africa and the Middle East carry the highest load, at 18.0% prevalence, while globally most cases remain confined to the earlier stages (1 through 3) rather than advanced disease.

The downstream toll is substantial too CKD was the ninth-leading cause of death and twelfth-leading cause of disability-adjusted life years in 2023, and it contributed to roughly 11.5% of cardiovascular deaths. Three metabolic drivers keep surfacing across analyses of this trend: elevated fasting blood glucose, high BMI, and raised systolic blood pressure[2].

According to a 2024 cohort study, drug-induced AKI represents a significant portion of cases at 19.3%, reinforcing the serious threat posed by nephrotoxic drugs. Across a group of 1,398 hospitalized patients, 35.8% received acute kidney support and the mortality rate reached 33.6%. Although patients with DI-AKI had a lower death rate than those with other AKI types, their demand for renal replacement therapy was equally high. Notably, vancomycin emerged as the most nephrotoxic, correlating with the greatest likelihood of both death and the need for advanced support [3].

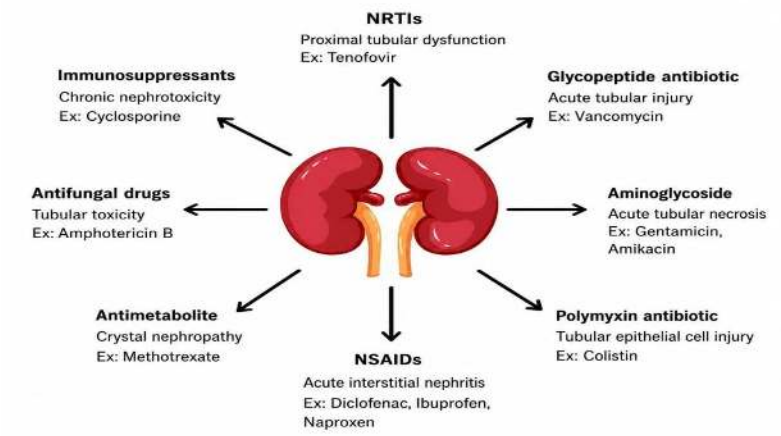


Figure 1: Representative of Drugs Associated with Each Mechanism

Experimental Animal models on Drug induced Renal Injury

Gentamicin induced Renal injury

When mice received daily intraperitoneal injections of gentamicin at 100 mg/kg for a period of 7 to 10 days, this treatment ultimately triggered acute tubular necrosis[12],In Rabbits a dose of 150 mg per kg per day was given single injection[13], In Hartley guinea pigs species are given with 80mg &100mg/ kg/ day via Subcutaneous route[14].

Advantages & Limitations[15]

From a practical standpoint, this model has a great deal going for it. It is technically uncomplicated, causes minimal distress to the animal, and delivers

exceptionally consistent results across repeated trials. The tubular injury it produces follows a clear dose-response relationship, and the core mechanisms-oxidative damage coupled with impaired mitochondrial function-have been thoroughly dissected over the years.

The dosages commonly used in experimental settings are often vastly higher than anything encountered in routine clinical practice. There is also the thorny issue of biological variability: mice appear remarkably resistant, which complicates cross-study comparisons and generalization. More fundamentally, the model operates in a vacuum that bears little resemblance to the complex reality of human patients-it overlooks coexisting illnesses, the confounding effects of multiple drug regimens, and the systemic upheaval caused by sepsis. On top of all that, the renal injury it induces is acute and short-lived, with spontaneous recovery occurring fairly quickly. This makes it ill-suited for exploring the protracted, progressive processes that define chronic kidney disease, limiting its utility to questions about early or reversible damage rather than long-term pathology.

Vancomycin induced Renal injury

Male Wistar rats were given vancomycin intraperitoneally over a period of seven days. In separate experiments, male Sprague-Dawley rats received either a single intravenous dose of vancomycin at 400 mg/kg or daily doses of 150 mg/kg for four days (96 hours) to produce kidney injury[16].

In rabbits, vancomycin-induced nephrotoxicity was induced by administering the drug intraperitoneally at 200 mg/kg twice daily for seven days[17]

Advantages & Limitations[16]

This model provides several important advantages: it demonstrates the relationship between dosing frequency and nephrotoxicity, enables direct comparisons of once-daily versus twice-daily vancomycin administration, and maintains tightly controlled experimental conditions with few confounding factors. It also allows for the assessment of both biochemical and histological indicators of renal injury, offering a consistent and reproducible preclinical platform for studying vancomycin-induced kidney damage.

The primary limitations include the possibility that results from rats may not translate directly to humans, given differences in kidney function and how vancomycin is processed in the body. The drug doses used in the experiment might not reflect typical clinical levels, and the model does not fully account for real-world conditions such as sepsis, fluid loss, or the use of other kidney-damaging medications. Moreover, the exact mechanism behind kidney damage may not be fully clarified, and standard markers of kidney injury could indicate problems only after significant damage has occurred. Lastly, the small number of subjects involved restricts how broadly the results can be applied.

Cisplatin induced Renal injury

In a study Sprague-Dawley rats were administered with cisplatin single intraperitoneal (IP) dose of of 8 mg/kg for 3 consecutive days to induce nephrotoxicity [18]. In this experiment, the animals were selected to be adult male New Zealand White rabbits. Single intraperitoneal (IP) injection of cisplatin at a dose of 4.0 and 6.5 mg/kg body weight was used. Animals were observed after receiving the medicine and on the third day, the degree of renal damage was determined to evaluate acute kidney damage[19]

Acute renal damage model induced by cisplatin was established on adult guinea pigs. Animals received single intraperitoneal (IP) injection of cisplatin at a dose of 5 mg/kg body weight to induce nephrotoxicity for 7 consecutive days[20]. Adult zebrafish (Danio rerio) were used to generate an experimental model of cisplatin-induced acute kidney injury. Specifically, nephrotoxicity was induced by intraperitoneal administration of the chemical at a dose of 20 µg per fish. In order to assess the extent of acute kidney injury, cisplatin-damaged kidneys were analyzed at 24-48 hours following treatment[21]

Advantages & Limitations[18]

In a study the . employed a cisplatin-induced kidney injury model in Sprague-Dawley rats, offering a consistent and reproducible system for studying acute nephrotoxicity. This model enables the evaluation of renal damage through a range of indicators, including biochemical parameters (creatinine, urea, NGAL),

markers of oxidative stress (MDA, CAT, TAS/TOS), and molecular factors (nephrin, synaptopodin, RAC1). Additionally, it facilitated exploration of TRPC5 signaling pathways and the potential protective effects of clemizole in mitigating cisplatin-related kidney injury.

The primary limitations include the use of a rat model, which may restrict how well the results can be applied to humans. The cisplatin dose of 8 mg/kg and the experimental setup might not closely resemble actual clinical treatment conditions. Additionally, the model does not account for various patient-specific factors such as pre-existing illnesses, dehydration, concurrent medications, or the presence of cancer. Since the study primarily examines acute kidney injury, its findings may not extend to long-term or chronic kidney damage.

Diclofenac induced Renal injury

The animals received diclofenac by oral gavage 100 mg/kg once a day for 3days to induce nephrotoxicity in male CD1 mice with subclinical acute kidney injury triggered by renal ischemia-reperfusion[22] .Adult New Zealand White rabbits were used to induce nephrotoxicity by administering diclofenac 10 mg/kg body weight by the intramuscular route once a day for 5 days [23].

Transgenic zebrafish embryos (Danio rerio , Tg (wt1b: EGFP) were used to evaluate nephrotoxicity at the developmental stage. At 24 hours post fertilization, embryos were incubated in embryo medium containing 25 μM diclofenac for 24 hours [24].

Advantages & Limitations[23]

The study indicates that diclofenac may worsen existing subclinical acute kidney injury (AKI) and contribute to its advancement toward chronic kidney disease (CKD). Functional and histological evaluations of the kidneys support this finding, revealing greater fibrosis and tubular damage following exposure to the drug.

The study involved a limited number of male mice, which limits the direct applicability of the results to humans. The doses of diclofenac and the ischemia-reperfusion model used may not accurately represent typical clinical scenarios. Additionally, the research did not include direct measurements of diclofenac concentrations in the blood or levels of renal prostaglandins.

Colistin induced Renal injury

Male Wistar rats were used to establish an experimental model of colistin-induced acute kidney injury. Renal toxicity by IP administration of colistin at a dose of 300,000 IU/kg/day once a day for 7 consecutive days [25]

New Zealand White rabbits was induced by a single intravenous loading dose of colistin sulfate followed by intramuscular injections for 7 consecutive days [26]. The nephrotoxicity of colistin was studied in zebrafish (Danio rerio) embryos. A water immersion method was used to expose 6 hour post-fertilization (hpf) embryos to 0, 0.01, 0.1, 1, 2, 3, and 10 μM colistin for 96 hours. The survival, embryonic morphology, lateral-line hair cell and epidermal keratinocyte were analyzed to evaluate the toxicity of colistin [27.]

Advantages & Limitations[25]

This experimental model offers a reliable and standardized platform for investigating nephrotoxicity induced by colistin. It facilitates the assessment of renal functional, biochemical, oxidative stress, inflammatory, and morphological alterations. Importantly, the model enables the exploration of underlying molecular mechanisms, specifically regarding autophagy and necroptosis via the AMPK/mTOR and RIPK1/RIPK3/MLKL cascades. Consequently, it serves as a valuable tool for elucidating the pathophysiology of colistin-related renal damage and for evaluating potential nephroprotective interventions, such as omega-3 nanoemulsion

However, several constraints must be acknowledged. Being an animal-based study, the direct applicability of the results to human clinical scenarios is limited. The experimental dosing regimens and treatment parameters are not fully representative of real-world patient exposures. Furthermore, the model fails to account for confounding clinical variables, including severe systemic infection, critical illness, pre-existing renal dysfunction, or polypharmacy. Lastly, the design primarily addresses acute injury, thereby restricting its relevance to chronic or progressive kidney disease

Amphotericin B induced Renal injury

A single intra-peritoneal injection of amphotericin B deoxycholate at a dose of 15mg/kg was administered to

male Wistar Albino rats to induce the condition. The animals were kept for a period of seven days[28]. Male C57BL/6 mice were injected with amphotericin B deoxycholate at a dose of 4mg/kg to induce the disease via an intra-venous route[29]

Advantages & Limitations[28]

The amphotericin B-induced nephrotoxicity model in Wistar rats provides a well-standardized and repeatable platform for investigating acute kidney injury. It consistently elicits distinct renal dysfunction, reflected by elevated blood urea nitrogen and creatinine levels, alongside overt structural damage such as tubular dilation and necrosis. Beyond these functional and morphological endpoints, this system enables comprehensive evaluation of oxidative stress, antioxidant enzyme responses, apoptotic signaling, and renal tissue integrity. These attributes render it particularly valuable for screening the nephroprotective potential of therapeutic candidates, as exemplified by dapagliflozin

Several significant constraints limit the interpretation of these findings. The study's reliance on a rat model raises questions about direct human applicability, while the use of a single 50 mg/kg amphotericin B dose across just seven days does not necessarily reflect real-world therapeutic exposure. Furthermore, dapagliflozin failed to produce meaningful changes in systemic oxidative-stress or apoptotic markers, undermining the evidence for the suggested protective pathways.

Tenofovir induced Renal injury

Male Wistar rats were induced by adding tenofovir disoproxil fumarate (TDF) to the standard diet strength of 300 mg/kg of food (approximately 30 mg/kg of body weight per day) for 45 consecutive days[30]. Male C57BL/6 mice were induced by oral gavage of TDF at a dose of 200, 500, or 800 mg/kg/day for 4 weeks [31].

Advantages & Limitations[30]

It provides a consistent method for studying kidney damage resulting from long-term drug use. It allows researchers to assess various aspects of renal health, including function, blood flow, oxidative stress, inflammation, cell death, and structural injury to tubules. In addition, examining key signaling pathways-such as SIRT1/Nrf2/HO-1, TLR4/NF-κB, and those involved in mitochondrial apoptosis-helps identify the mechanisms driving kidney injury and aids in evaluating dapagliflozin's potential protective effects on the kidneys.

The major limitations of the study are that the research was conducted among male Wistar rats, which cannot represent the human population. The experiment was carried out using a single dose of 45-day tenofovir exposure and experimental doses; thus, the results do not consider the clinical setting. Moreover, there were only six to eight animals per group, which is a relatively small sample size. Even though dapagliflozin was proved to be beneficial in terms of organ functions and molecular processes, the study is preclinical, and there is a need for clinical trials to approve the drug for the treatment of tenofovir nephrotoxicity.

Cyclosporine A induced Renal injury

In male Wistar rats, cyclosporine A was delivered intraperitoneally at 20 mg/kg/day over seven consecutive days, leading to nephrotoxicity[32]. In New Zealand White rabbits, cyclosporine A (CsA) was given subcutaneously at 25 mg/kg/day, divided into two doses per day, for five consecutive days[33].

Advantages & Limitation[32]

The cyclosporine A-induced nephrotoxicity model offers a standardized approach for investigating kidney injury in male Wistar rats. It permits assessment of renal function, oxidative imbalance, inflammatory responses, apoptosis, and histopathological alterations through various biochemical and molecular markers. This model is therefore valuable for understanding the mechanisms underlying cyclosporine-related renal damage and for testing potential protective treatments such as sitagliptin and hesperidin.

The major limitations of the study include the use of male rats as subjects which limits the applicability of the results to both genders. Another limitation is the high dosage of cyclosporine used which may not be applicable in clinical practice. The study also used a small sample size to conduct the experiment which limits the accuracy of the results. Lastly, the study focused on the acute effects of cyclosporine on the

kidney which limits the applicability of the results in understanding the effects of long-term use of the drug.

Methotrexate induced Renal injury

Male Wistar albino rats were produced by a IP of methotrexate (20 mg/kg) on the 5th day of a 10-day experiment [34] . Male mice were used Nephrotoxicity was induced by methotrexate in combination with omeprazole for 48, resulting in renal tubular damage, oxidative stress, and apoptosis [35] . Adult rabbits were induced by IP of methotrexate at a dose of 20 mg/kg body weight for 14 days [36]

Advantages & Limitations[34]

The methotrexate-induced nephrotoxicity model may be employed to study the acute nephrotoxicity of methotreaxate. The model enables to assess kidney function and structure, and the influence of the drug on the tubules, endothelium, podocyte morphology, and the ratio between pro-apoptotic BAX and anti-apoptotic BCL2 proteins. Moreover, using this model it is possible to evaluate the nephroprotective effect of L-carnitine against methotrexate-induced toxicity through the analysis of oxidative stress and apoptosis.The significant limitations of the present study include the use of female Wistar rats as a model which may limit applicability to humans and males.

Tabular form of experimental animals models is shown in Table 1

Drug	Animals	Dose (mg/kg/day)	Route	Duration
Gentamicin	Male Mice[12]	100mg/kg	I.P	7-10 days.
	Male Adult Rabbits[13]	150mg/kg	Single injection	4 hours
	Male Hartley Guineapig[14]	80mg &100mg/kg	Subcutaneous S.c.	14 days
Vancomycin	Male Sprague-Dawley rats[15]	150 mg/kg,	Intravenous I.V	4 Days
	Male& Female Rabbits[17]	200 mg/kg twice daily	I.P	7 Days
Cisplatin	Male Sprague-Dawley rats[18]	8mg/kg	I.P	3 days
	Male New Zealand White rabbits[19]	4.0 mg/kg & 6.5 mg/kg,	I.P	3 days
	Adult Guinea pigs[20]	5 mg/kg,	I.P	7 Days
	Adult zebrafish[21] (Danio rerio)	120 µg/ml	I.P	24-48 hours
Diclofenac	Male Sprague-Dawley rats[22]	10 mg/kg	I.P	5 days
	Adult New Zealand White rabbits[23]	10 mg/kg	Intramuscular	5 days
	Transgenic zebrafish (Danio rerio)[24]	25 µM diclofenac	Immersion	24hours
Colistin	Male Wistar rats[25]	300,000 IU/kg	I.P	7 days
	Adult NewZealand White rabbits[26]	150,000&300,000 IU/kg	IM	7 days
	Zebrafish (Danio rerio)[27]	10 µM	I.P	4 days
Amphotericin B	Male Wistar albino rats[28]	15 mg/kg	I.P,	7 days
	Male C57BL/6 mice[29]	4mg/kg	I.V	7 days
Tenofovir	Male Wistar rats[30]	600mg/kg	Oral	45 days
	Male C57BL/6 mice[31]	800 mg/kg	Oral	28 days
Cyclosporine A	Male Wistar rats[32]	20 mg/kg	I.P.	7 days
	Male mice[33]	30mg/kg	S.C.	28 days
Methotrexate	Male Wistar albino rats[34]	20 mg/kg,	I.P	10 days
	Male mice[35]	300 mg/kg	I.P	48 hours
	Male Adult rabbits[36]	20 mg/kg	I.P	14 days

Biomarkers of Renal injury

Classification of Biomarkers[37] shown in Table 3

Serum Creatinine

The most commonly used functional biomarker currently is serum creatinine (SCr). Creatinine, a by product of creatine in skeletal muscle, is typically excreted through glomerular filtration in the kidneys. A decrease in creatinine clearance results in increased serum levels of creatinine. Serum creatinine is a standard clinical laboratory marker for acute kidney injury (AKI). There are several limitations to using SCr for determining AKI development. First, SCr usually rises more than 24-48 hours after an acute decline in kidney function, making it inadequate for the early detection of AKI. It may altered by a number of factors, including age, gender, muscularity, diet, and fluid balance[38].

Blood Urea Nitrogen

One of the biomarkers that can be used to indicate the function of the kidneys is blood urea nitrogen (BUN). It determines the amount of nitrogen that is obtained from urea. The liver is responsible for producing urea as a by-product when breaking down protein; approximately 30% is reabsorbed in the renal tubules following glomerulus filtration. However, BUN levels are often unreliable since it can be easily altered by fluid intake and output, liver function, bleeding, and increased production of protein in the body. Thus, blood urea nitrogen is not used exclusively to evaluate kidney injury due to its inconsistency. Creatinine and newer markers for kidney injury are used alongside BUN to determine renal dysfunction because BUN levels increase much later after kidney injury and are easily influenced by other factors[39]

KIM-1 -Kidney Injury Molecule-1

One of the sensitive structural indicators KIM-1.The gene product is significantly up-regulated in the proximal tubular epithelial cells during damage but is barely detectable in normal kidneys. Like NGAL.It is a good indicator for the early recognition and assessment of AKI because it rises early after injury before the increase in serum creatinine[40.]

NGAL- Neutrophil Gelatinase-Associated Lipocalin

The 25-kDa glycoprotein is called (NGAL) and is minimally expressed in healthy kidneys, but it is strongly increased in renal tubular epithelial subsequent to kidney injury. The protein is released into the circulation and urine within 2-6 hours after nephrotoxic or ischemia injury. It is an early indicator of tubular injury, enabling timely treatment, unlike the serum creatinine, which usually rises . The severity of kidney damage is directly correlated with the amount of urinary NGAL and plasma NGAL. Moreover, the levels can help predict the recovery of kidney function and the clinical outcome[41]

TNF-α -Tumor Necrosis Factor-alpha

TNF-α was evaluated as pro-inflammatory biomarker for its association with acute kidney injury (AKI). The study established that AKI patients had distinctly higher levels relative to healthy individuals, suggesting that increased TNF-α levels are linked to more severe renal inflammation. Moreover, higher TNF-α levels were associated with poor clinical outcomes and disease severity. Therefore, TNF-α is a potential prognostic and diagnostic biomarker for AKI and plays an essential role in disease pathology[42]

IL-6 - Interleukin-6

(IL-6) is rapidly produced during the occurence of (AKI). Notably, the elevation of circulating IL-6 levels is strongly correlated with the degree of renal damage, severity of inflammation, and overall poor outcome, including mortality. Therefore, IL-6 can be considered as a reliable prognostic biomarker, particularly during the first 24-72 hours after AKI onset. Indeed, in a murine model of nephrotoxic kidney damage, IL-6 was prominently induced, whereas the expression of klotho protein was reduced, which was sufficient to ameliorate IL-6-triggered manifestations and protect against kidney injury[43]

MCP-1 - Monocyte Chemoattractant Protein-1

It is an inflammatory chemokine, which is significantly increased during the early stages of AKI. Early on following the an injury, it might be seen in the urine., which makes it a promising biomarker for the diagnosis of disease. Compared to some traditional

biomarkers of kidney injury, urinary MCP-1 is more specific since its levels are rarely elevated due to uremia[44].

MDA - Malondialdehyde

A major marker of oxidative stress is malondialdehyde (MDA), which reflects the degree of lipid peroxidation. The augmented production of MDA is initiated by excessive formation of ROS that attack cellular membranes, especially those of the kidney, causing injury. More prominent manifestations of AKI or CKD are related to increased level of MDA in serum or kidney tissue, which is considered to be a reliable oxidative stress biomarker[45].

GSH -Reduced Glutathione

As one of the most potent intracellular antioxidants that plays a critical role in protecting renal cells from oxidative damage is glutathione (GSH). Decreased levels of this substance are associated with the progression of kidney disease since oxidative stress provokes increased lipid peroxidation leading to cell damage. its use led to a decrease in blood urea nitrogen and malondialdehyde in serum while reducing the damage to renal tissues and suppressing ferroptosis [46]

SOD-Superoxide Dismutase

It neutralizes superoxide radicals by transforming them into oxygen and hydrogen peroxide. Elevated oxidative stress reduces SOD activity, thereby worsening kidney damage. This study found a strong link between the advancement of AKI and levels of urinary SOD1 as well as overall SOD activity. As a result, SOD1 shows potential as a biomarker for identifying severe AKI[47].

Table 3: Classification of Biomarkers[37]

Functional Biomarkers	**Serum Creatinine (SCr)**
	BUN - Blood Urea Nitrogen
	Serum Cystatin C (Cysc)
Structural biomarkers	KIM-1 Kidney Injury Molecule-1
	NGAL-Neutrophil Gelatinase-Associated Lipocalin
	NAG - N-Acetyl-β-D-Glucosaminidase
	L-FABP - Liver-Type Fatty Acid-Binding Protein
	Clusterin
Inflammatory biomarkers	IL-18 -Interleukin-18
	TNF-α -Tumor Necrosis Factor-alpha
	IL-6 - Interleukin-6
	MCP-1 - Monocyte Chemoattractant Protein-1
Oxidative stress biomarkers	MDA - Malondialdehyde
	GSH -Reduced Glutathione
	SOD -Superoxide Dismutase
	CAT - Catalase
	GPx - Glutathione Peroxidase.

Future prospects

Looking ahead, progress in drug-induced renal injury research depends on creating preclinical systems that more faithfully mirror human kidney biology, thereby addressing the frequent disconnect between animal study outcomes and clinical reality. Innovative platforms-including kidney organoids derived from human stem cells and microphysiological organ-on-a-chip devices-hold significant promise by more accurately replicating renal architecture and function. These systems allow researchers to examine how different cell types respond to toxic insults, explore genetic influences on susceptibility, and investigate drug metabolism within a tightly controlled setting. When coupled with artificial intelligence and machine learning tools, these models are improving the prediction of nephrotoxic risk during early-stage drug discovery, leveraging chemical structure data and gene expression profiles to

flag potential hazards and elucidate underlying mechanisms with growing precision. At the same time, the push to clinically validate and regulatorily endorse newer urinary biomarkers-such as KIM-1, NGAL, and emerging candidates like vanin-1 and microRNAs-is enabling identification of renal damage at much earlier stages, frequently before conventional indicators like serum creatinine register any abnormality. Future efforts will also prioritize the convergence of multi-omics profiling, advanced imaging modalities, and personalized medicine frameworks to account for the complex interplay of genetic variants, biological sex, and concurrent drug therapies that shape individual vulnerability to nephrotoxic effects. Additionally, ongoing initiatives to harmonize experimental protocols and reduce dependence on animal models through New Approach Methodologies are expected to bolster both the reproducibility and ethical integrity of preclinical investigations. Together, these converging innovations are poised to accelerate the translation of laboratory discoveries into clinical practice, ultimately strengthening patient protection and diminishing the overall impact of medication-related kidney damage

REFERENCES

1. Connor S, Li T, Qu Y, Roberts RA, Tong W. Generation of a drug-induced renal injury list to facilitate the development of new approach methodologies for nephrotoxicity. Drug Discov Today. 2024;29 (4):103938. doi:10.1016/j.drudis.2024.103938
2. GBD 2023 Chronic Kidney Disease Collaborators. Global, regional, and national burden of chronic kidney disease in adults, 1990-2023, and its attributable risk factors: a systematic analysis for the Global Burden of Disease Study 2023. Lancet. 2025;406 (10518):2461-82. doi:10.1016/S0140-6736 (25)01853-7.
3. Garcia, G., Pacchini, V. R., Zamoner, W., Balbi, A. L., & Ponce, D. (2024). Drug-induced acute kidney injury: A cohort study on incidence, identification of pathophysiological mechanisms, and prognostic factors. Frontiers in Medicine, 11, 1459170 doi.org/10.3389/fmed.2024.1459170
4. Pabla N, Dong Z. Cisplatin nephrotoxicity: mechanisms and renoprotective strategies. Kidney Int. 2008;73 (9):994-1007. doi:10.1038/sj.ki.5002786.
5. Lodise TP, Lomaestro B, Graves J, Drusano GL. Larger vancomycin doses (at least four grams per day) are associated with an increased incidence of nephrotoxicity. Antimicrob Agents Chemother. 2008;52 (4):1330-6. doi:10.1128/AAC.01602-07.
6. Whelton A. Nephrotoxicity of nonsteroidal anti-inflammatory drugs: physiologic foundations and clinical implications. Am J Med. 1999;106 (5B):13S-24S. doi:10.1016/S0002-9343 (99)00113-8.
7. Pogue JM, Lee J, Marchaim D, Yee V, Zhao JJ, Chopra T, et al. Incidence of and risk factors for colistin-associated nephrotoxicity in a large academic health system. Clin Infect Dis. 2011;53 (9):879-884.
8. Laniado-Laborín R, Cabrales-Vargas MN. Amphotericin B: side effects and toxicity. Rev Iberoam Micol. 2009;26 (4):223-227. doi:10.1016/j.riam.2009.06.003.
9. Hall AM, Hendry BM, Nitsch D, Connolly JO. Tenofovir-associated kidney toxicity in HIV-infected patients: a review of the evidence. Am J Kidney Dis. 2011;57 (5):773-780.
10. Naesens M, Kuypers DRJ, Sarwal M. Calcineurin inhibitor nephrotoxicity. Clin J Am Soc Nephrol. 2009;4 (2):481-508. doi:10.2215/CJN.04800908.
11. Perazella MA. Crystal-induced acute renal failure. Am J Med. 1999;106 (4):459-65. doi:10.1016/S0002-9343 (99)00041-8
12. Fu Y, Xiang Y, Wei Q, Ilatovskaya D, Dong Z. Rodent models of AKI and AKI-CKD transition: an update in 2024. Am J Physiol Renal Physiol. 2024 Apr 1;326 (4):F563-F583. doi: 10.1152/ajprenal.00402.2023. Epub 2024 Feb 1. PMID: 38299215; PMCID: PMC11208034.
13. Kojima T, Kobayashi T, Iwase S, Matsumura T. Gentamicin nephrotoxicity in young rabbits. Exp Pathol. 1984;26 (2):71-75. doi:10.1016/S0232-1513 (84)80072-9.

14. Comparative ototoxicity of gentamicin in the guinea pig and two strains of rats. Hear Res. 1987;31 (2):161-167. doi:10.1016/0378-5955 (87)90122-5.
15. Randjelovic P, Veljkovic S, Stojiljkovic N, Sokolovic D, Ilic I. Gentamicin nephrotoxicity in animals: Current knowledge and future perspectives. EXCLI J. 2017 Mar 24;16:388-399. doi: 10.17179/excli2017-165.
16. Konishi H, Morita Y, Mizumura M, Iga I, Nagai K. Difference in nephrotoxicity of vancomycin administered once daily and twice daily in rats. J Chemother. 2013;25 (5):273–278. doi:10.1179/1973947812Y.0000000067.
17. Ali S, Qaisarani M, Farhat K, Waheed A. Study of preventive effect of melatonin on high dose vancomycin induced nephrotoxicity in rabbits. Pak Armed Forces Med J. 2018;68 (6):1625-1629.
18. Kumaş-Kulualp M, Gepdiremen A, Karataş E, Eşrefoğlu M. Clemizole hydrochloride, a potent TRPC5 calcium channel inhibitor, prevents cisplatin-induced nephrotoxicity in Sprague-Dawley rats. J Biochem Mol Toxicol. 2023;37 (7):e23372. doi:10.1002/jbt.23372.
19. Abdel-Gayoum AA, Ahmida MHS. Changes in the serum, liver, and renal cortical lipids and electrolytes in rabbits with cisplatin-induced nephrotoxicity. *Turk J Med Sci.* 2017;47 (3):1019-1027. doi:10.3906/sag-1602-136.
20. Durak I, Ozbek H, Karaayvaz M, Ozturk HS. Cisplatin induces acute renal failure by impairing antioxidant system in guinea pigs: effects of antioxidant supplementation on the cisplatin nephrotoxicity. Drug Chem Toxicol. 2002;25 (1):1–8. doi:10.1081/DCT-100108468.
21. Morales Fénero C, Padovani BN, do Amaral MA, et al. Acute Kidney Injury Model Induced by Cisplatin in Adult Zebrafish. Journal of Visualized Experiments (JoVE). 2021; (171). DOI: 10.3791/61575
22. Störmer J, et al. A Single Oral Dose of Diclofenac Causes Transition of Experimental Subclinical Acute Kidney Injury to Chronic Kidney Disease. Biomedicines. 2022;10 (5):1198. https://doi.org/10.3390/biomedicines10051198
23. El-Shafei DA, El-Gendy KS. Protective effect of antioxidants against diclofenac-induced nephrotoxicity in rabbits. Journal of Applied Toxicology. 2015;35 (9):1047–1055.
24. Westhoff JH, Steenbergen PJ, Thomas LSV, et al. In vivo High-Content Screening in Zebrafish for Developmental Nephrotoxicity of Approved Drugs. Frontiers in Cell and Developmental Biology. 2020;8:583. doi:10.3389/fcell.2020.00583.
25. Taha M, El-Bassossy HM, Elberry AA, Abdelsalam RM, et al. Insights into the protective effect of omega-3 nanoemulsion against colistin-induced nephrotoxicity in experimental rats: Regulation of autophagy and necroptosis via AMPK/mTOR and RIPK1/RIPK3/MLKL signaling pathways. Renal Failure. 2024;46 (1):2434559. doi:10.1080/0886022X.2024.2434559. PMID: 39584420.
26. Bader Z, Waheed A, Hashim R. Establishment and comparison of nephrotoxicity associated with the use of various doses of colistin in rabbits: Nephrotoxicity with colistin in rabbits. Pakistan Armed Forces Medical Journal. 2016;66 (2):180–184.
27. Yen HJ, Lin JR, Yeh YH, Horng JL, Lin LY. Exposure to colistin impairs skin keratinocytes and lateral-line hair cells in zebrafish embryos. Chemosphere. 2021;263:128241.
28. Kaya B, Avci C, Ates KE, et al. Protective effect of dapagliflozin against Amphotericin B-induced nephrotoxicity in an experimental rat model. Scientific Reports in Medicine. 2025. doi:10.37609/srinmed.56.
29. Shen L, Song Y, Xiao Y, et al. Early and Stable Mouse Model of Amphotericin B-Induced Acute Kidney Injury: Application of Continuous Non-Invasive GFR Monitoring. Clin Exp Pharmacol Physiol. 2025;52 (10):e70071. doi:10.1111/1440-1681.70071.
30. dos Santos VA, Viotto ACR, Nascimento MM, Bernardo DRD, Shimizu MHM, de Sena CR, et al. Dapagliflozin treatment ameliorates oxidative

stress, apoptosis and inflammation in tenofovir-induced nephrotoxicity in rats. Sci Rep. 2025;15:43706. doi:10.1038/s41598-025-27555-z.

31. Jiang Y, Zhang Y, Zheng Y, Zhang L, Wang X, Li H, et al. Renal dysfunction and tubulopathy induced by high-dose tenofovir disoproxil fumarate in C57BL/6 mice. Healthcare (Basel). 2020;8 (4):417. doi:10.3390/healthcare8040417.
32. Abd-Eldayem AM, Makram SM, Messiha BAS, Abd-Elhafeez HH, Abdel-Reheim MA. Cyclosporine-induced kidney damage was halted by sitagliptin and hesperidin via increasing Nrf2 and suppressing TNF-α, NF-κB, and Bax. *Scientific Reports*. 2024;14:7434. doi:10.1038/s41598-024-57300-x.
33. Prévot A, Mosig D, Guignard JP. Acute cyclosporine A-induced nephrotoxicity: a rabbit model. Pediatr Nephrol. 2000;14 (6):498–503. doi:10.1007/s004670050793.
34. Türkoglu Ö, Usta Z, Çavdarlı K, Garlı S, Alp N. L-Carnitine attenuates methotrexate-induced nephrotoxicity by modulating BAX/BCL2 apoptotic signaling and preserving podocyte, endothelial, and tubular integrity. J Appl Toxicol. 2026. doi:10.1002/jat.70096.
35. Wei X, Yu J, Gao JZ, Xu ZK, Jiang X, Shen WW, et al. GRK2 dysfunction mediates acute kidney injury in murine administered methotrexate combined with omeprazole. Acta Pharmacol Sin. 2026;47 (1):148-161. doi:10.1038/s41401-025-01602-x.
36. Talukder S, Islam S, Islam S, Akanda MR, et al. Protective role of silymarin against methotrexate induced nephropathy in rabbits. J Biochem Toxicol. 2025. doi:10.1002/jbt.70544.
37. Vaidya VS, Ferguson MA, Bonventre JV. Biomarkers of acute kidney injury. Annu Rev Pharmacol Toxicol. 2008;48:463-493. doi:10.1146/48.113006.094615.
38. Parikh CR, Coca SG, Thiessen-Philbrook H, Shlipak MG, Koyner JL, Wang Z, et al. Postoperative biomarkers predict acute kidney injury and poor outcomes after adult cardiac surgery. J Am Soc Nephrol. 2011;22 (9):1748-57. doi:10.1681/ASN.2010121302.
39. Canney M, Clark EG, Hiremath S. Biomarkers in acute kidney injury: On the cusp of a new era? J Clin Invest. 2023;133 (13):e171431. doi:10.1172/JCI171431.
40. Yang C, Xu H, Yang D, Xie Y, Xiong M, Fan Y, et al. A renal YY1-KIM1-DR5 axis regulates the progression of acute kidney injury. Nat Commun. 2023;14 (1):4261. doi:10.1038/s41467-023-40036-z.
41. Marakala V. Neutrophil gelatinase-associated lipocalin (NGAL) in kidney injury – A systematic review. Clin Chim Acta. 2022;536:135–141 doi:10.1016/j.cca.2022.08.029
42. Imoto K, Tanaka M, Goya T, Azuma Y, Hioki T, Aoyagi T, et al. Acute kidney injury is an unfavorable prognostic factor in acute liver failure and is associated with tumor necrosis factor-alpha. Medicine (Baltimore). 2023;102 (45):e35931. doi:10.1097/MD.0000000000035931.
43. González-Lafuente L, Mercado-García E, Vázquez-Sánchez S, et al. Interleukin-6 as a prognostic marker in acute kidney injury and its klotho-dependent regulation. Nefrología (English Edition). 2024;44 (6):818–829.DOI: 10.1016/j.nefroe.2024.11.010
44. Munshi R, Johnson A, Siew ED, et al. MCP-1 Gene Activation Marks Acute Kidney Injury. Journal of the American Society of Nephrology. 2011;22 (1):165–175.DOI: 10.1681/ASN.2010060641
45. Noels H, Jankowski V, Schunk SJ, Vanholder R, Kalim S, Jankowski J. Post-translational modifications in kidney diseases and associated cardiovascular risk. Nat Rev Nephrol. 2024;20 (8):495–512. doi:10.1038/s41581-024-00837-x.
46. He L, Shi Y. Reduced glutathione ameliorates acute kidney injury by inhibiting ferroptosis. Molecular Medicine Reports. 2023;27 (6):123. doi:10.3892/mmr.2023.13011.
47. Holthoff JH, Harville Y, Herzog C, Juncos LA, Karakala N, Arthur JM. SOD1 is a novel prognostic biomarker of acute kidney injury following

cardiothoracic surgery. BMC Nephrology. 2023;24 (1):299. doi:10.1186/s12882-023-03350-8.

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