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Review IJTT

Drug Induced Immune Mediated Nephritis: Molecular Mechanism, Pathways, and Clinical Implications

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Abstract

Drug-induced immune-mediated nephritis (DI-IMN) has become a more widely known cause of acute kidney injury (AKI), with the potential for development to chronic kidney disease if not detected and treated promptly. T-cell hypersensitivity to pharmaceuticals, such as antibiotics, proton pump inhibitors, nonsteroidal anti-inflammatory drugs, and immunological drugs, are the major causes for it. Beyond clinical burden, DI-IMN reflects intricate molecular interactions that sustain interstitial inflammation and tubular injury. These interactions include haptenization and neoantigen creation, antigen presentation, costimulatory signaling, and cytokine–chemokine networks. Conventional biomarkers, such as proteinuria and serum creatinine, are not sensitive enough to detect early diseases. Novel urine and serum indicators (such as soluble CD163, NGAL, MCP-1, and KIM-1) and multi-omics techniques provide better phenotyping, therapy monitoring, and earlier detection. Renal biopsy with immunophenotyping remains the diagnostic cornerstone, but the combination of genetic profiling, pharmacogenomics, and AI-based risk models promises more precise, less intrusive approaches. This review synthesizes epidemiology, immunopathogenesis, and drug-specific patterns of DI-IMN, highlighting diagnostic challenges and translational opportunities. We emphasize early drug withdrawal and timely immunosuppression to enhance renal recovery, along with reno-protective measures. Future directions focus on personalized medicine, and real-time monitoring is required to mitigate long-term renal morbidity and improve patient outcomes who are exposed to high-risk medications.

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INTRODUCTION

Burden of Drug Induced Immune Mediated Nephritis

One important and frequently overlooked category of adverse medication reactions affecting the kidneys is drug-induced immune-mediated nephritis (DI-IMN). Drug-induced acute interstitial nephritis (DI-AIN), the most common type, is an immune-mediated hypersensitivity reaction that causes an inflammatory infiltration of the renal interstitium and tubules, often leading to acute kidney injury (AKI) with potential long-term consequences if left untreated. Antibiotics, proton pump inhibitors, NSAIDs, and immune checkpoint inhibitors are among the most often implicated drug classes in DI-AIN, which accounts for 0.5%–3% of all kidney biopsies and up to 5%–27% of biopsies performed for AKI [1, 2].

Beyond interstitial tubulitis, drug-induced nephritis has a significant epidemiological impact. Pharmacovigilance data show that drug-related acute kidney damage and interstitial nephritis are becoming more common worldwide, especially as targeted treatments and immunotherapies, like immune checkpoint inhibitors, become more widely used. 32,722 reports of acute kidney injury and 2,056 reports of tubulointerstitial nephritis linked to anticancer medications were found in the WHO VigiBase database from 1967 to 2023. Compared to other drug classes, immunotherapy showed the strongest disproportionate reporting signal for interstitial nephritis [3].

Clinically, these disorders significantly increase morbidity, the need for medical treatment, and the risk of developing chronic renal disease. DI-AIN generally manifests as nonspecific AKI, frequently without typical allergy symptoms, delaying diagnosis and possibly requiring renal biopsy for confirmation. Immune-mediated kidney damage can result in chronic renal failure and a higher risk of end-stage renal disease if it is not quickly detected and the offending medication is stopped. To lessen the burden of this severe adverse medication effect, these realities highlight the significance of increased clinical awareness, early pharmacovigilance, and risk mitigation techniques [4].

Need for Molecular Level Understanding

Immune mechanisms including hapten production, antigen presentation, and T-cell-mediated hypersensitivity reactions are the main causes of drug-induced immune-mediated nephritis (DI-IMN), which most frequently present drug-induced acute interstitial nephritis. When drugs or their metabolites attach to renal tubular proteins, they create neoantigens that trigger cellular immune reactions and cause interstitial inflammation. Histopathologic investigations consistently show that the renal interstitium is infiltrated with activated lymphocytes, macrophages, and cytokines, highlighting the disease's immunological rather than merely toxic nature. Therefore, enhancing diagnostic precision and therapeutic decision-making requires an understanding of these molecular and immunopathological pathways [5].

Importance of Early Detection of (DI-IMN)

Due to the close correlation between permanent renal damage and the development of chronic kidney disease and continuing exposure to the offending drug, early identification of DI-IMN is crucial. Early diagnosis is difficult since clinical signs are sometimes ambiguous and traditional hypersensitivity symptoms are frequently lacking. Biomarkers that indicate tubular damage or immune activity may allow for prompt intervention prior to the development of severe fibrosis. Therefore, the disease burden, morbidity, and long-term renal consequences linked to immune-mediated medication toxicity may be considerably decreased by incorporating molecular diagnostics into clinical practice [6].

Despite advances in pharmacovigilance, significant gaps persist in translating molecular insights into clinical practice for DI-IMN. This review aims to comprehensively elucidate the molecular mechanisms, diagnostic challenges, and emerging biomarkers of drug-induced immune-mediated nephritis (DI-IMN), with a focus on high-risk drug classes (e.g., antibiotics, PPIs, NSAIDs, ICIs), to inform early detection strategies and mitigate long-term renal morbidity in clinical practice.

MOLECULAR INSIGHTS

The focus on molecular discoveries in DI-IMN is strongly justified by clinical case series, cohort studies, and mechanistic research. Studies supported by biopsies show that T-cell-mediated immune damage predominates, with interstitial infiltration of CD4 and CD8 cells, activation of macrophages, and elevated expression of pro-inflammatory cytokines such interleukin-17, interferon-γ, and tumor necrosis factor-α [7]. Immunological checkpoint inhibitor case studies further illustrate how pharmacologic immunological tolerance disruption triggers renal autoimmunity, which has molecular and histologic characteristics with traditional drug-induced nephritis [8]. Concurrently, advances in biomarker research have revealed early markers of immune-mediated tubular injury, such as soluble CD163, neutrophil gelatinase-associated lipocalin (NGAL), monocyte chemoattractant protein-1 (MCP-1), and urinary kidney injury molecule-1 (KIM-1), which frequently increase prior to discernible

changes in serum creatinine. These results highlight the need of molecular profiling for early diagnosis, distinguishing acute kidney damage from other causes, and directing tailored treatment [9].

RATIONALE FOR FUTURE RESEARCH AND CLINICAL TRANSLATION

Reducing the long-term clinical burden of drug-induced immune-mediated nephritis requires a concentrated focus on molecular causes and early detection techniques. Early drug withdrawal coupled with prompt corticosteroid therapy greatly enhances renal recovery and lowers the chance of developing chronic kidney disease, according to observational studies and systematic reviews [10]. On the other hand, prolonged interstitial inflammation, fibrosis, and permanent nephron loss are linked to delayed recognition. Immune signatures and molecular biomarkers may help with early risk assessment, lessen reliance on invasive kidney biopsies, and allow for individualized treatment plans when included into standard clinical practice. Additionally, new transcriptome and proteomic research supports a move toward predictive and preventive nephrology by highlighting the potential of genetic tools to monitor disease activity, forecast vulnerability, and evaluate therapy response [11].

OVERVIEW OF DRUG INDUCED IMMUNE MEDIATED NEPHRITIS

Acute Interstitial Nephritis (AIN)

The most common kind of drug-induced immune-mediated nephritis is acute interstitial nephritis, which is characterized by inflammatory infiltration of the tubules and renal interstitium with relative sparing of the blood vessels and glomeruli. It is mostly caused by a delayed type IV hypersensitivity reaction involving drug-specific T lymphocytes, which results in interstitial edema and lymphocyte, plasma cell, macrophage, and frequent eosinophil infiltration. Proton pump inhibitors, immune checkpoint inhibitors, nonsteroidal anti-inflammatory medications (NSAIDs), and antibiotics (β-lactams, fluoroquinolones) are common offending agents [12]. Acute kidney injury, sterile pyuria, mild to moderate proteinuria, and rarely systemic symptoms including fever, rash, and eosinophilia are the clinical manifestations of AIN. Early detection and stopping the offending medication are essential because delayed diagnosis can lead to chronic renal disease and permanent interstitial fibrosis [13].

Drug Induced Glomerulonephritis

Immune-mediated damage that mainly affects the glomerular capillary tuft and is caused by immune complex deposition, in situ antibody production, or complement activation is referred to as drug-induced glomerulonephritis. Depending on the underlying immunological mechanism, the pathological patterns could include crescentic glomerulonephritis, membranous nephropathy, or mesangial proliferative glomerulonephritis. Gold salts, penicillamine, interferons, anti-TNF medicines, and certain chemotherapeutic medications have all been linked to drug induced glomerular nephritis [14].

Drug Induced Vasculitis Associated Nephritis

Anti-neutrophil cytoplasmic antibodies (ANCA) are frequently linked to drug-induced vasculitis-associated nephritis, a severe immune-mediated disease marked by inflammation of small blood vessels. On histology, it most commonly manifests as quickly progressing glomerulonephritis with crescent development. Well-known triggers include medications like hydralazine, propylthiouracil, minocycline, allopurinol, and cocaine tainted with levamisole. Endothelial damage, neutrophil activation, and drug-induced autoantibody production are all part of the pathophysiology. Clinically, individuals may have lung bleeding, fever, arthralgia, and rapidly deteriorating renal function. To avoid irreparable renal damage and systemic consequences, immunosuppressive therapy must be started as soon as the offending medication is stopped [15].

Lupus Like Nephritis

Like lupus nephritis but without idiopathic systemic lupus erythematosus, lupus-like nephritis is a unique immune-complex-mediated kidney damage. Anti-double-stranded DNA antibodies, hypocomplementemia, and a “full-house” immunofluorescence pattern on kidney biopsy are its defining characteristics [16]. Hydralazine, procainamide, isoniazid, and anti-TNF biologics are the medications most frequently linked to this illness. Long-term medication exposure causes autoantibody formation and immunological tolerance

loss, which is the pathogenic mechanism. Clinically, patients generally have systemic lupus-like symptoms along with proteinuria, hematuria, and variable degrees of renal impairment. Drug-induced lupus-like nephritis, in contrast to idiopathic lupus nephritis, frequently gets better after stopping drugs, albeit in extreme situations, immunosuppressive treatment could be necessary [17].

EPIDEMEOLOGY OF DRUG INDUCED NEPHRITIS

About 10–20% of intrinsic acute kidney damage (AKI) in hospitalized patients is caused by drug-induced immune-mediated nephritis, which primarily manifests as acute interstitial nephritis (AIN). It is the primary cause of biopsy-proven AIN globally. According to epidemiological data, the incidence has increased over the past few decades, primarily due to increased pharmaceutical exposure, polypharmacy in older populations, and improved diagnostic knowledge. More than two-thirds of AIN cases are reliably linked to pharmaceuticals, according to current biopsy series. Delays in identification often result in partial renal recovery and the development of chronic kidney disease. Significantly, the underappreciated impact of this syndrome in clinical practice has been reinforced by the trend in recognition toward biopsy-based diagnosis due to the lack of traditional hypersensitivity characteristics in many patients [18].

Commonly Implicated Drug Classes

Immune-mediated nephritis is regularly linked to several medication groups. The most common triggers are still antibiotics, especially β-lactams, fluoroquinolones, rifampicin, and sulfonamides, which usually cause T-cell-mediated delayed hypersensitivity reactions. Proton pump inhibitors (PPIs), which frequently have a subacute or subtle presentation and few extrarenal symptoms, have become a major cause worldwide. Nonsteroidal anti-inflammatory medicines (NSAIDs) are frequently linked to concurrent glomerular damage and nephrotic-range proteinuria in older people. As the range of drug-related immune renal damage has expanded, immune checkpoint inhibitors used in cancer treatment have been more well-known in recent years as a unique cause of autoimmune-type interstitial nephritis. Immune activation that targets tubular antigens continues to be the primary pathogenic mechanism across medication classes [19].

Immunopathogenic Mechanism Underlying Drug-Induced Nephritis

Haptenization and Neoantigen Formation

Haptenization, in which low-molecular-weight medications or their reactive metabolites bind covalently to native kidney proteins to generate neoantigens, is one of the key processes behind drug-induced immune-mediated nephritis. The immune system recognizes these modified self-proteins as foreign, triggering an adaptive immune response. Because of the kidney's high drug exposure and metabolic activity, tubular epithelial cells are especially sensitive. Immune sensitization results from neo-antigen production, which encourages local antigen-presenting cells to absorb and process antigens. This mechanism, which offers a mechanistic explanation for the delayed onset of clinical disease after drug exposure, is extensively reported for β-lactam antibiotics, NSAIDs, and proton pump inhibitors [20].

Drug Specific T-Cell Activation

T-cell-mediated delayed hypersensitivity reactions (type IV) are the main cause of drug-induced nephritis. Through either direct pharmacological interaction with immune receptors (the p-i idea) or hapten-dependent processes, drug-derived antigens activate $CD4^+$ and $CD8^+$ T cells. Tubular epithelial cells are directly harmed by cytotoxic mediators released by activated T cells that penetrate the renal interstitium. Dense interstitial T-cell infiltration is frequently seen in renal biopsy specimens, confirming the crucial function of cell-mediated immunity. Further emphasizing the critical role of T-cell dysregulation in disease pathogenesis, immune checkpoint inhibitors constitute a novel paradigm in which loss of immunological tolerance results in unchecked T-cell activation against renal antigens [21].

Role of Antigen Presenting Cells and Costimulatory Signals

Immune-mediated kidney damage is initiated and amplified by antigen-presenting cells (APCs) such as macrophages and dendritic cells. Within renal tissue and secondary lymphoid organs, these cells

digest drug-associated antigens and deliver them to naïve T lymphocytes via major histocompatibility complex (MHC) molecules. In addition to antigen recognition, costimulatory signals like CD80/CD86–CD28 interactions are necessary for effective T-cell activation. T-cell proliferation is increased and inflammation is sustained when costimulatory molecules are upregulated in inflammatory renal tissue. In immune checkpoint inhibitor-associated nephritis, where inhibitory immunological checkpoints are pharmacologically suppressed, dysregulation of these pathways is most noticeable [22].

Cytokine and Chemokine Network Driving Renal Inflammation

As illustrated in Figure 1, complex cytokine and chemokine networks that encourage immune cell recruitment and tissue damage prolong the inflammatory cascade in drug-induced nephritis. Pro-inflammatory cytokines, like interleukin-17, interferon-γ, and tumor necrosis factor-α, are released by activated T cells and macrophages, which exacerbate interstitial inflammation and tubular damage. Mononuclear cell migration into the renal interstitium is facilitated by chemokines such as CCL2 (MCP-1) and CXCL10. Fibrosis and partial renal recovery are caused by persistent activation of these pathways, especially when medication cessation or immunosuppressive therapy is postponed [22].

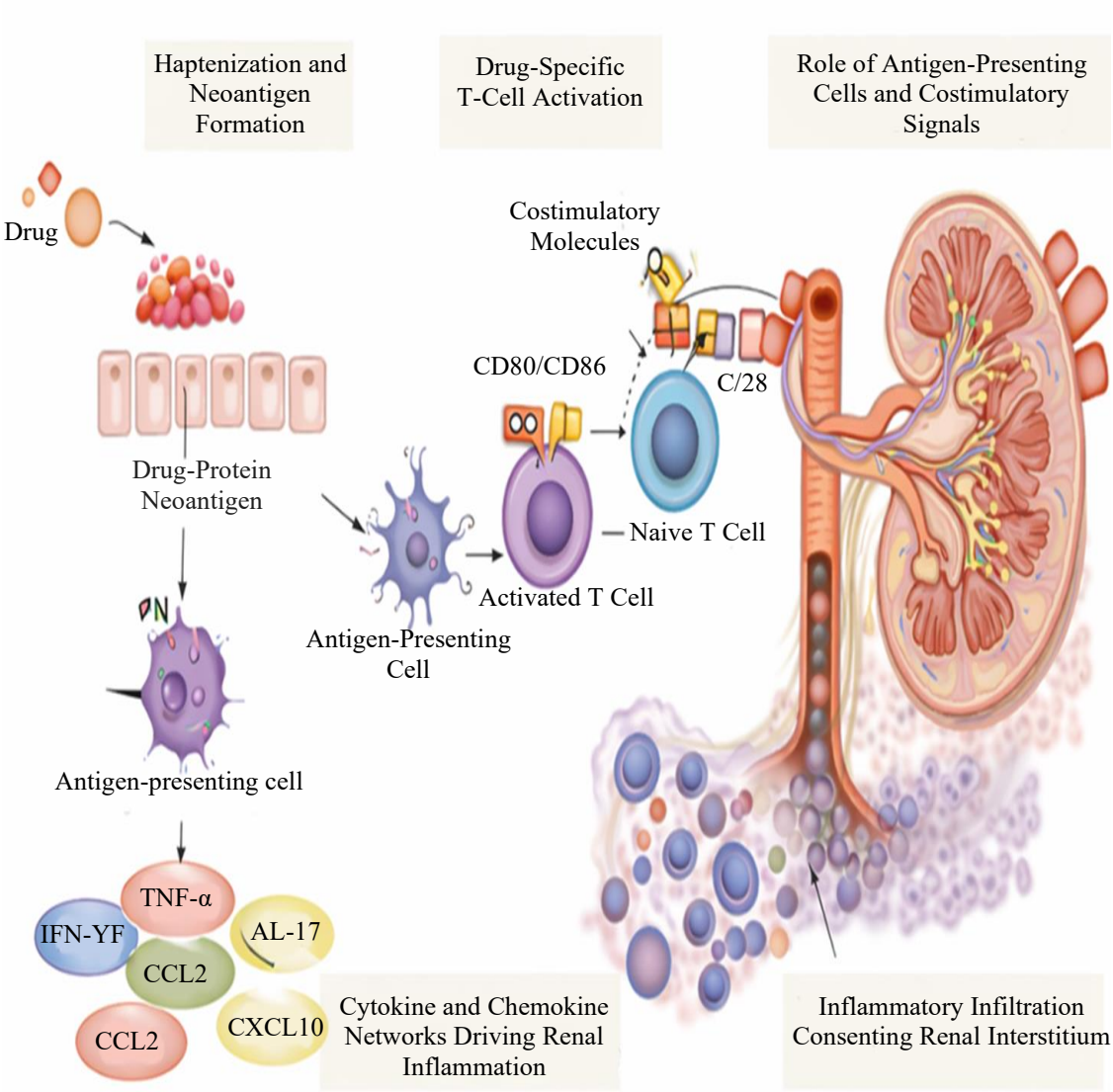

Figure 1. Schematic of DI-IMN pathogenesis: drug haptens form renal neoantigens, activate APCs and drug-specific t-cells via CD28/CD80/86, releasing TNF-α, IFN-γ, and chemokines to drive interstitial inflammation.

Molecular and Cellular Pathway of Renal Immune Injury

Immune signaling induced by drugs plays pivotal role in the genesis of immune mediated nephritis. Figure 2 depicts the downstream signaling in drug/infection/antigen exposure, etc. in IMN.

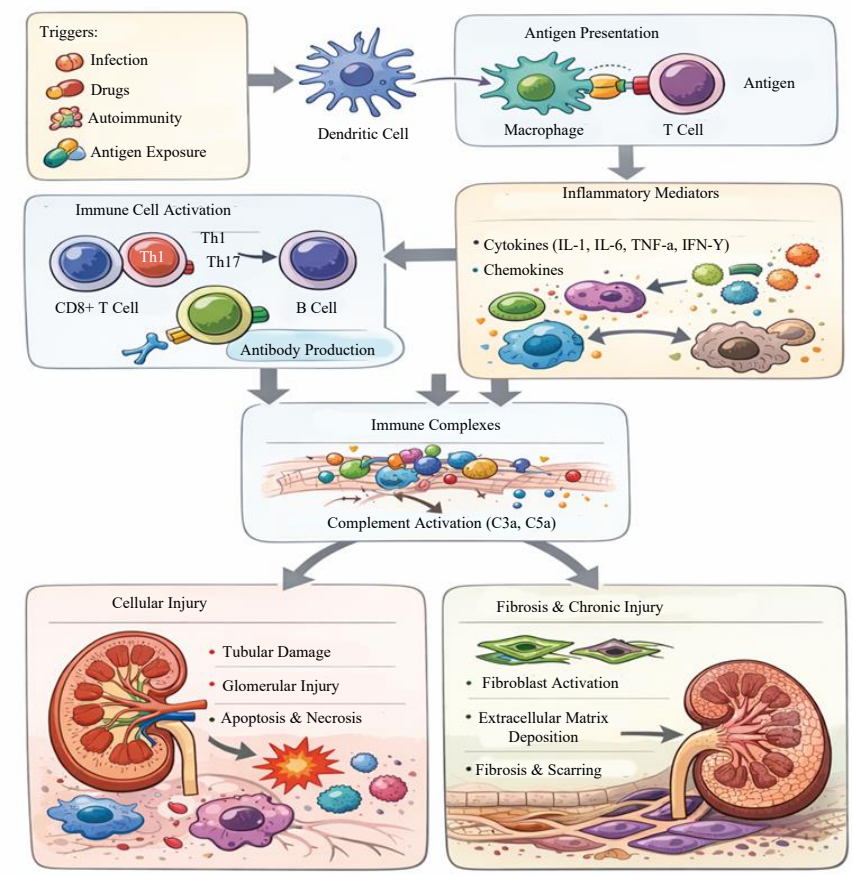

Figure 2. Molecular and cellular pathway of renal immune injury [23].

Innate Immune Signaling

Innate immune signaling constitutes an early and critical pathway in renal immune injury. Pattern-recognition receptors, particularly Toll-like receptors (TLRs) expressed on tubular epithelial cells, macrophages, and dendritic cells, sense drug-induced danger signals and activate downstream inflammatory pathways, including NF-κB signaling. Concurrently, activation of inflammasomes, such as NLRP3 promotes the maturation and release of interleukin-1β and interleukin-18, amplifying interstitial inflammation and tubular injury. Complement activation further exacerbates renal damage by enhancing leukocyte recruitment, endothelial dysfunction, and local inflammatory amplification. Together, these innate immune pathways establish a pro-inflammatory renal microenvironment that facilitates subsequent adaptive immune activation [24].

Adaptive Immune Responses

Adaptive immune responses play a central role in sustaining renal inflammation and tissue injury. $CD4^+$ T-helper cell subsets, particularly Th1 and Th17 cells, produce interferon-γ and interleukin-17, respectively, driving macrophage activation and perpetuating tubular and interstitial damage. In parallel, B-cell activation may contribute to immune-mediated renal injury through autoantibody production and immune complex formation, especially in lupus-like or glomerular patterns of drug-induced nephropathy. The persistence of these adaptive immune mechanisms explains the chronicity of inflammation and the progression toward fibrosis when immune activation is not adequately controlled [25].

Role of Renal Resident Cells

Renal resident cells actively participate in immune-mediated kidney injury rather than serving as passive targets. Tubular epithelial cells respond to inflammatory stimuli by releasing cytokines, chemokines, and adhesion molecules that promote immune cell recruitment and retention within the interstitium. Podocytes are susceptible to immune-mediated injury, leading to cytoskeletal disruption and proteinuria, while endothelial cells contribute to inflammation by facilitating leukocyte adhesion, complement activation, and microvascular dysfunction. The dynamic interaction between immune cells and renal parenchymal cells sustains inflammation and promotes fibrotic remodeling, ultimately contributing to incomplete renal recovery [23].

Genetic and Epigenetic Susceptibility Factors

Genetic factors are traits or differences in an individual's DNA (genes) acquired from parents that may affect the likelihood of illness development. These include gene mutations, polymorphisms, or variations in specific genes. Susceptibility factors are conditions or characteristics that elevate the probability of disease development, although they do not ensure it. The HLA, the most polymorphic area of the human genome, is linked to numerous kidney illnesses; some are immune-mediated, while in others the pathophysiology remains ambiguous or the significance of HLA is less defined. Advances in molecular methodologies and the application of model systems have elucidated the mechanistic foundations of HLA connections and, in certain cases, have especially connected HLA to other genes [26].

Epigenetic Modifications Influencing Immune Activation

The immune system's growth and operation are significantly influenced by epigenetic mechanisms. DNA methylation, histone modifications, and noncoding RNAs are examples of epigenetic modifications that play a major role in the pathophysiology of autoimmune disorders by controlling gene expression. The word "epigenetics" refers to the meiotically/mitotically heritable variations in gene expression that are caused by environmental stimuli without affecting the DNA's base sequence. Epigenetic alterations are kept as additional regulators in immune responses because genome-wide profiling sometimes fails to provide an adequate explanation for the intricate biological processes in autoimmune diseases (Figure 3). By controlling immune cell activities, epigenetic dysregulation has a direct impact on the emergence of autoimmunity [27].

Drug Specific Patterns of Immune Mediated Nephrotoxicity

Immune-mediated nephrotoxicity is not dose dependent and occurs due to hypersensitivity or immune activation, most commonly presenting as acute interstitial nephritis (AIN) or immune-mediated glomerular disease [28]. Table 1 shows the drug's class, toxicity pattern and mechanism of toxicity induction.

Table 1. Drug-induced nephrotoxicity – patterns and mechanisms.

Drug class	Nephrotoxicity pattern	Mechanism
NSAIDs, Beta-lactams, PPIs, Diuretics, Antibiotics	Acute interstitial nephritis	Hypersensitivity-mediated immune reactions.
Hydralazine, Procainamide, Sulfadiazine	Drug-induced lupus, ANCA-associated GN, immune complex deposition	Autoantibody formation & immune complex deposition.
Targeted Therapies (TKIs, anti-VEGF)	Thrombotic microangiopathy, proteinuria	Endothelial injury with complement activation.
Chemotherapy Agents	Tubular injury, ATIN patterns	Direct toxicity & immune responses in some settings.
Immune Checkpoint Inhibitors (e.g., PD-1/PD-L1, CTLA-4)	Acute interstitial nephritis (AIN), glomerulonephritis, vasculitis	Immune activation, loss of tolerance, T-cell infiltration and cytokine-mediated inflammation.

By enhancing anti-tumor immunity through cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed death-1/programmed death-ligand 1 (PD-1/PD-L1), immune checkpoint inhibitors

(ICI) transformed cancer treatment. Renal problems are among the immune-related adverse effects (irAEs) that come with this innovation. Complex mechanisms, such as auto-reactive T cells, auto-antibodies, drug-specific T cell reactivation, and cytokine-driven inflammation, leading to AKI are involved in ICI-related nephritis. Usually appearing weeks to months into therapy, ICI-AKI frequently coexists with other irAEs. It has been introduced to effectively block tumor cells' immune evasion, creating a pro-inflammatory tumor microenvironment that may improve disease control [29].

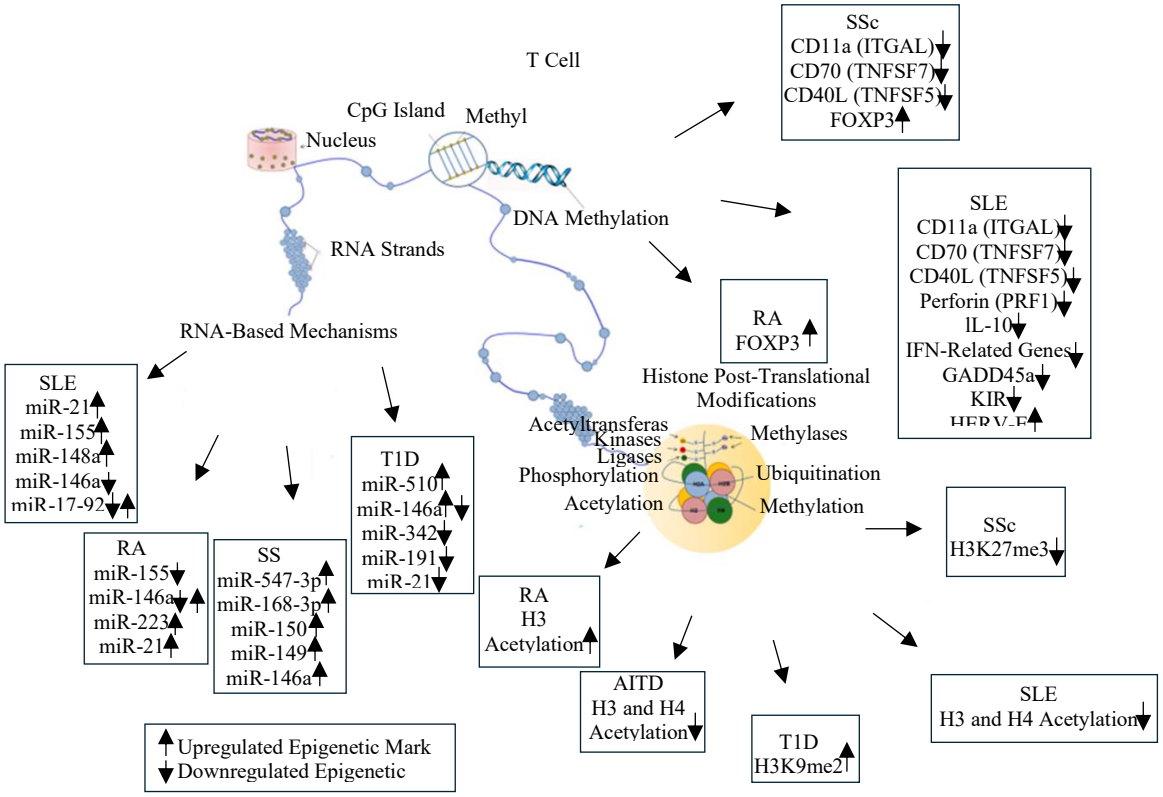

Figure 3. Schematic representation of key epigenetic mechanism involved in the pathogenesis of autoimmune diseases, including SLE, RA, SSc, SS, AITD, and T1D.

BIOMARKERS FOR EARLY DETECTION OF IMMUNE-MEDIATED NEPHRITIS

Conventional Biomarkers and Limitations

For early immune-mediated kidney damage, conventional indicators like proteinuria, blood urea nitrogen, and serum creatinine lack sensitivity and specificity. Rather than early immune activation, these signs frequently indicate established kidney injury [30].

Emerging Urinary and Serum Biomarkers

Cytokines, chemokines, and tubular damage indicators are examples of novel biomarkers that show promise for immune-mediated nephritis early identification and surveillance. These indicators could shed light on the course of the illness and the effectiveness of treatment [31].

Omics-Based Approaches

Proteomics, transcriptomics, and metabolomics are examples of high-throughput omics technologies that allow for thorough analysis of molecular alterations linked to immune-mediated nephritis. These methods make it easier to find disease-specific markers and possible treatment targets [32].

DIAGNOSTIC STRATEGIES AND RISK SATISFACTION

Clinical and Histopathological Correlations

As clinical manifestations such proteinuria, hematuria, and renal dysfunction do not always reliably indicate the underlying renal pathology, clinical-histopathological correlation is crucial in the diagnosis

and management of nephritis. Studies has shown that though certain clinical patterns – such as nephrotic syndrome with minimal change disease or membranous nephropathy, nephritic presentations with IgA nephropathy, and severe renal impairment with proliferative lupus nephritis – tend to correlate with specific histological lesions, these correlations are not always consistent. Histological classification and activity/chronicity indices have a stronger correlation with renal prognosis in lupus nephritis than do clinical features alone. As a result, renal biopsy is still essential for precise nephritis diagnosis, treatment selection, and prognosis [33].

Role of Renal Biopsy and Immunophenotyping

Despite advances in molecular and serological markers, renal biopsy has remained significant for the accurate diagnosis, classification, and prognostic of nephritis over the last five to six years. In the glomerular, tubulointerstitial, and vascular compartments, biopsy-based histopathology offers vital information on disease activity, chronicity, and pattern of injury that cannot be accurately determined from clinical criteria alone, according to recent investigations. By precisely identifying immune deposits (including IgG subclasses, IgA, and complement components like C3 and C1q) and inflammatory cell profiles, immunophenotyping using immunofluorescence and immunohistochemistry has grown in significance [34]. This has improved disease classification and pathogenic understanding. Recent research shows that cellular immune signatures and immune deposit patterns are highly correlated with treatment responsiveness and long-term renal outcomes in lupus nephritis and IgA nephropathy. In addition, emerging techniques which connect tissue immunophenotyping with peripheral blood immune profiling and molecular techniques point to a potential future for better disease monitoring and biopsy-guided individualized therapy. Therefore, renal biopsy in conjunction with sophisticated immunophenotyping remains the cornerstone of evidence-based clinical decision-making in contemporary nephritis therapy [35].

Predictive Models and AI-Based Risk Assessment

To enhance early detection, risk stratification, and personalized prognosis of kidney inflammation and related conditions, such as chronic kidney disease (CKD), lupus nephritis, and acute kidney injury (AKI), recent nephrology studies are increasingly utilizing artificial intelligence (AI) and machine learning (ML) models. By combining clinical, laboratory, and biomarker data, advanced predictive models – like XGBoost, Random Forest, CatBoost, and neural networks – have been developed to identify patients at high risk of disease progression, flare-ups, and unfavorable outcomes, frequently with high accuracy and discriminative performance [36]. For instance, proactive therapies have been made available by the successful stratification of lupus nephritis flare risk into discrete risk categories using AI frameworks utilizing urinary biomarkers. While models utilizing electronic medical records and multi-omics data show promise in personalized risk prediction and treatment advice, techniques, such as explainable AI (XAI) and ensemble learning, enhance interpretability and clinical trust. Despite these advances, there still exist problems with clinical integration, model interpretability, external validation, and the ethical use of patient data (Tables 2 and 3). This emphasizes the need for more research before normal application in clinical practice [37].

Table 2. Predictive model performance in glomerulonephritis classification [38].

Model	Validation AUC	Test AUC	Notes
Support Vector Machine (SVM)	0.82	0.82	Good baseline performance.
Random Forest (RF)	0.87	0.89	Best overall in study.
AdaBoost (ADB)	0.86	0.88	Comparable to RF.
Physician clinical diagnosis	0.55	0.59	Significantly lower than AI models.

Table 3. Applications of AI/ML models in kidney diseases [39].

Scenario	AI technique	Method	Disease focus
ESRD prediction in IgA nephropathy	Supervised learning	XGBoost	Kidney disease.
AKI continuous prediction	Deep learning	RNN	Acute kidney injury.
Diabetic glomerulosclerosis classification	CNN & unsupervised	Deep learning	Chronic kidney disease.

PREVENTION STRATEGIES AND THERAPEUTIC INTERVENTIONS

Drug Selection, Dose Optimization, and Treatment Duration

The underlying reason, histology, severity, and progression risk each impact the choice of medications for nephritis. Glucocorticoids in combination with mycophenolate mofetil or cyclophosphamide are frequently used in induction therapy for immune-mediated nephritis, especially lupus nephritis, because these regimens have greater remission rates than steroids alone. To improve efficacy and lower steroid exposure, biologics, like belimumab and calcineurin inhibitors like tacrolimus and voclosporin, are also used frequently [40]. Azathioprine or mycophenolate mofetil should be used for maintenance following remission.

While corticosteroids or more recent medications (such as endothelin receptor antagonists) are only used in high-risk individuals with IgA nephropathy, supportive therapy with ACE inhibitors or ARBs is still fundamental. The main treatment for acute interstitial nephritis is stopping offending medication; short-term corticosteroids are used to speed up renal recovery. The principal objective of evidence-based, guideline-directed medication selection is to strike a balance between long-term safety, kidney preservation, and immunosuppressive efficacy [41].

Dose Optimization

Acute Interstitial Nephritis – Steroid Dose & Duration (Table 4)

Optimal Dose

- *Initial Prednisone:* ~0.8–1 mg/kg/day (max ~60 mg/d) is commonly recommended.
- Some protocols consider 0.5–1 mg/kg/day especially in less severe cases.
- IV methylprednisolone pulse therapy can be used in severe presentations before oral steroids, but evidence doesn't show superiority in all cases.

Table 4. Therapy regimen of steroids in various stages of nephritis.

Condition	Typical initial steroid dose	Duration of high-dose phase	Total treatment duration
Acute Interstitial Nephritis	~0.8–1 mg/kg/day prednisone	~2–3 weeks	~6–8 weeks total taper
Lupus Nephritis (Induction)	IV pulses + 0.35–1 mg/kg/day oral	Months (taper over months)	Part of ≥36 months total therapy
Lupus Nephritis (Maintenance)	Low-dose steroids + immunosuppressant's	–	≥36 months

Treatment Duration

- High-dose steroids are typically given for 2–3 weeks, followed by tapering over several weeks (total ~6–8 weeks).
- Extending high-dose therapy beyond ~3 weeks or total steroid duration >8 weeks has not shown improved kidney recovery and may increase side effects.
- Early initiation (soon after diagnosis or drug withdrawal) is more critical than longer duration — delays correlate with poorer recovery.

Clinical Evidence Summary

- One retrospective cohort (n = 182) found median high-dose steroid duration ~2 weeks and total therapy ~9 weeks, with no benefit for >3 weeks high-dose or >8 weeks total duration in terms of renal recovery [42].

Lupus Nephritis (LN) – Immunosuppression Dose & Duration

Lupus nephritis is a glomerular immune-mediated nephritis requiring more prolonged immunomodulation than AIN.

General Treatment Phases

Treatment is divided into two phases:

- Induction (initial) – intense therapy to control active disease.
- Maintenance (subsequent) – lower-intensity therapy to prevent relapse.

Induction Phase: Glucocorticoids

- IV methylprednisolone pulses (e.g., 250–1000 mg/day for 1–3 days) often used initially in moderate-to-severe LN.
- Followed by oral prednisone ~ 0.35–1.0 mg/kg/day (not exceeding ~80 mg/d) with gradual taper over months.

Immunosuppressive Agents

Commonly combined with steroids for induction:

- Mycophenolate mofetil (MMF/MPA).
- Cyclophosphamide (IV or oral).
- Calcineurin inhibitors (e.g., tacrolimus or voclosporin).
- Belimumab as adjunct in certain scenarios.

Dosing and combinations vary by histologic class and clinical severity – , e.g., class III/IV often requires more intensive regimens.

Maintenance Phase & Duration

The latest 2024 KDIGO recommendations emphasize long-term immunosuppression:

Treatment Duration

- Total duration of immunosuppression (induction + maintenance) ≥ 36 months (3 years) for proliferative LN.
- This is based on data showing higher relapse risk if therapy is withdrawn earlier.

Glucocorticoid Tapering

- Prednisone is tapered to low doses — ≤5 mg/day by ~6 months — to balance efficacy vs toxicity.

Maintenance Immunosuppressant Dosing

Typical maintenance doses include:

- *MMF:* ~750–1000 mg twice daily.
- *MPA:* ~540–720 mg twice daily.

Low-dose glucocorticoids may continue alongside these agents [43].

IgA Nephropathy/Other Glomerular Nephritides (Example)

Clinical research in IgA nephropathy suggests optimizing corticosteroid dose (e.g., full dose vs half dose) with adjunctive immunosuppressants is under study, though definitive dosing strategies vary by protocol and trial design (Table 4) [44].

Pharmacogenomics Screening and Patient Stratification

Patient stratification in nephritis becomes easier by pharmacogenomic (PGx) screening, which identifies genetic variations that affect toxicity, immunological response, and medication metabolism [45]. Different reactions to corticosteroids, immunosuppressants (azathioprine, cyclophosphamide, mycophenolate), and biologics used in lupus nephritis and other immune-mediated nephritides have been linked to variations in genes such ABCB1, IL-10, TNF, MIF, ITPA, and HLA loci. PGx-guided stratification promotes personalized therapy and dose optimization by categorizing patients into high-toxicity risk groups, non-responders, or likely responders [46]. Studies from nephrology and more general PGx clinical settings demonstrate that genetically tailored treatment and better communication of results are associated with better treatment confidence, fewer adverse drug reactions, and higher

patient satisfaction, suggesting indirect benefits in nephritis care, despite the lack of direct nephritis-specific patient satisfaction data [47].

Immunomodulatory Approaches and Renoprotective Strategies

The primary component of nephritis treatment is still immunomodulatory medication, especially for immune-mediated types like lupus nephritis and IgA nephropathy. By inhibiting pathogenic T- and B-cell activation and immune-complex-mediated inflammation, corticosteroids in combination with traditional immunosuppressants, like cyclophosphamide or mycophenolate mofetil (MMF), effectively induce remission [48]. Rituximab (anti-CD20) and belimumab (anti-BAFF), another two current targeted biologics, improve renal response rates in refractory disease in modifying B-cell survival and autoantibody synthesis. By stabilizing podocyte cytoskeletons and suppressing the immune system, calcineurin inhibitors – particularly tacrolimus and voclosporin – reduce proteinuria. Renoprotective measures, such as rigorous blood pressure control, proteinuria reduction, and renin-angiotensin-aldosterone system (RAAS) blocking, are essential to slowing the progression of chronic kidney disease [49]. Independent of immunologic activity, SGLT2 inhibitors and enhanced lipid and metabolic control have also been shown to be effective supplementary renoprotective strategies. Together, strong renoprotective care and focused immunomodulation enhance long-term renal survival in nephritis [50].

Monitoring and Surveillance in High-Risk Patients

Longitudinal Biomarker Monitoring

In nephritis, especially lupus nephritis (LN), longitudinal biomarker monitoring is vital for predicting prognosis, treatment response, and disease activity. Traditional serum markers, like complement levels (C3, C4) and anti-double-stranded DNA (anti-dsDNA) antibodies, are commonly employed and exhibit an acceptable link with flares when monitored over time, but they are not sensitive enough to detect early relapses. Reduction at 6–12 months is closely linked to improved renal survival, and serial measurement of proteinuria continues to be the best validated predictor of long-term renal prognosis [51]. Urinary biomarkers have been more popular for long-term evaluation in recent years because they more accurately indicate persistent intrarenal inflammation. Urinary MCP-1 (CCL2), NGAL, TWEAK, VCAM-1, and KIM-1 are examples of markers that show dynamic alterations prior to clinical flare-ups and decrease with treatment response. While measuring disease activity over time, composite urinary biomarker panels perform better than individual indicators. A precision-medicine approach is supported by emerging studies that integrate biomarker trajectories with histology and clinical indices, allowing for improved risk classification in nephritis and early diagnosis of subclinical activity [52].

Integration of Digital Health and Real-Time Alerts

Digital Health Integration in Chronic Kidney Disease (CKD)

Real-time monitoring of renal biomarkers, blood pressure, and medication adherence in chronic kidney disease (CKD) is made available by digital health technologies such as wearable biosensors, telemedicine, mobile health applications, and AI-driven clinical decision support systems. Despite ongoing issues with data security and scalability, these solutions provide proactive remote management, individualized risk stratification, and early illness progression detection [53].

Real-Time Alerts for Acute Kidney Injury (AKI)

Acute kidney injury (AKI), a frequent side effect of nephritis, is increasingly being identified using real-time electronic alert (e-alert) systems integrated into electronic health records. Such alerts improve the rates of nephrology referrals, AKI detection, and recording. Although consistent mortality benefits have not been demonstrated, systematic evaluations show a decrease during AKI (DOI: 10.1001/jamanetworkopen.2024.30401). Previous reviews emphasize how alert-based decision support and prediction algorithms might enhance physician response [54].

Nephritis and Real-Time Digital Health Tools

New digital tools designed for nephrology, such smartphone apps for managing nephrotic syndrome, provide real-time monitoring of clinical parameters, relapse identification, and compliance with medications, expanding alert-based care beyond AKI to chronic nephritis. While highlighting the need

for more solid data on long-term patient outcomes, consensus statements from the 27th Acute Disease Quality Initiative advocate the use of digital health and real-time alerts for early kidney injury identification and workflow improvement [55].

Multidisciplinary Management Approaches

Immune-mediated nephritis, including lupus nephritis and quickly progressing glomerulonephritis, requires multidisciplinary care. Nephrologists, rheumatologists, renal pathologists, clinical pharmacists, specialized nurses, and allied health professionals work together to provide coordinated treatment that guarantees precise diagnosis, right interpretation of kidney biopsy results, and optimal immunosuppressive therapy. Clinical pharmacists assist in reducing drug-related issues and enhancing adherence, whereas renal pathologists use histological categorization and activity/chronicity markers to direct therapy intensity. Monitoring, patient education, and psychological needs are supported by social workers, nutritionists, and specialist nurses. Research from multidisciplinary lupus nephritis clinics shows better adherence to protocols, shorter kidney biopsy delays, and more reliable clinical judgment, especially in complicated or resistant cases [56].

FUTURE DIRECTIONS AND RESEARCH GAPS

Translational Challenges

Gap from Target Discovery to Clinical Success

Many molecular targets identified in preclinical nephritis models fail to transition into effective therapies in humans. This reflects poor predictive validity of some animal models and complexities in human disease phenotypes (e.g., immune-mediated kidney disease) [57].

Clinical Trial Design & Surrogate Endpoints

Designing randomized controlled trials (RCTs) that show clear efficacy is difficult due to disease heterogeneity, small effect sizes, high costs, and lack of universally accepted surrogate endpoints in nephritis subtypes like lupus nephritis [58].

Disease Heterogeneity and Biomarkers

Renal diseases, especially autoimmune forms, like lupus nephritis, have diverse pathogenic mechanisms. Reliable biomarkers to stratify patients, monitor response, and predict outcomes are still under development [59].

Translating Mechanistic Insights into Therapies

Even when pathways (e.g., immune checkpoints, podocyte stress responses) are elucidated experimentally, translating these into safe, effective clinical therapies remains slow. Example: integration of immune modulation findings into new treatments requires overcoming regulatory and biological hurdles [60].

Integrated Clinical and Translational Frameworks

Symposium updates emphasize the need to unify basic science, clinical data, and therapeutic innovation to tackle complex syndromes like systemic lupus erythematosus with nephritis involvement [61].

Personalized Medicines in Drug-Induced Nephritis

The main objective of personalized medicine in drug-induced nephritis (DIN) is to customize treatment, diagnosis, and prevention according to each patient's genetic risk, immunological phenotype, and drug-exposure traits. High-risk patients can be identified before exposure thanks to pharmacogenomic associations (e.g., HLA-B58:01* with severe cutaneous responses and interstitial nephritis associated to allopurinol; HLA-DQA1/DRB1 alleles with antibiotic-induced AIN) [62]. Urinary markers (NGAL, KIM-1, MCP-1) and immunological signatures are used in biomarker-guided techniques that enhance early separation of DIN from other causes of AKI and may direct steroid responsiveness. To minimize overtreatment while maintaining renal recovery, personalized medication management also includes selective immunosuppression duration based on biopsy results and recovery kinetics, avoidance of re-challenge based on causality scores (RUCAM/ALDEN), and dose adjustment using real-time eGFR trajectories [63].

CONCLUSION

Drug-induced immune-mediated nephritis is an important and underrecognized cause of acute and chronic kidney injury, primarily driven by dysregulated immune mechanisms rather than direct toxicity. This review underscores the central role of hapten formation, T-cell activation, cytokine-driven inflammation, and loss of immune tolerance in shaping the diverse clinical and histopathological manifestations of disease. The rising use of immunotherapies, targeted agents, and polypharmacy has further increased the global burden of immune-mediated renal injury.

Advances in molecular biology, immunophenotyping, biomarker discovery, and multi-omics technologies have significantly enhanced understanding of disease pathogenesis and opened new avenues for early diagnosis and risk stratification. Despite these developments, renal biopsy remains the diagnostic cornerstone, particularly in complex or refractory cases. Early recognition, prompt withdrawal of the offending drug, and timely initiation of appropriate immunosuppressive therapy are critical determinants of renal recovery.

Future progress will depend on integrating molecular diagnostics, pharmacogenomics, artificial intelligence, and multidisciplinary care into routine clinical practice. A precision-medicine approach offers the greatest potential to improve outcomes, reduce chronic kidney disease progression, and optimize individualized therapy in drug-induced immune-mediated nephritis.

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