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REVIEW

# Neutrophils in Kidney Disease: Linking Neutrophil Function and Microenvironment to Therapeutic Targets

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**Abstract:** Neutrophils are central mediators of kidney immunity and injury, exerting both protective and pathogenic functions on tissue compartment, inflammatory response, and disease state. During urinary tract infection and pyelonephritis, neutrophils protect the host through phagocytosis, granule release, reactive oxygen species (ROS) production, and neutrophil extracellular trap (NET) formation. In contrast, dysregulated neutrophil activation contributes to sterile and autoimmune kidney disease, including cholesterol crystal embolism, anti-neutrophil cytoplasmic antibody -associated vasculitis (AAV), ischemic acute kidney injury, and progression to chronic kidney disease. Emerging evidence indicates that neutrophil function in the kidney is highly compartment-specific and shaped by local metabolic and inflammatory cues. Persistent neutrophil activation promotes thromboinflammation, endothelial injury, autoimmunity, and fibrogenic remodeling through release of cytokines, S100A8/A9, proteases, ROS, and NET-associated mediators. In chronic kidney disease, uremic toxins and metabolites, such as uric acid, further alter neutrophil function by impairing antimicrobial responses while sustaining inflammatory activation. This review summarizes current insights into neutrophil biology across infection, sterile, and autoimmune kidney diseases, with focus on complement-specific neutrophil functions and effector mechanisms. In addition, we discuss emerging therapeutic strategies targeting neutrophil activation pathways and highlight recent advances in spatial transcriptomics, single-cell technologies, and intravital imaging that are reshaping our understanding of neutrophil-mediated kidney injury.

**Keywords:** neutrophils, kidney injury, ANCA-associated vasculitis, complement, neutrophil extracellular traps, AKI-to-CKD transition

## Introduction

The kidneys receive approximately 20% of cardiac output and contain a highly specialized glomerular and peritubular microvascular network that is continuously exposed to circulating leukocytes, immune complexes, pathogens, and inflammatory mediators.[1] Hypertension, diabetes, and aging progressively impair this microvascular architecture through arteriolar hyalinosis, capillary rarefaction, glomerulosclerosis, podocyte loss, and nephron depletion; thereby increasing susceptibility to acute kidney injury (AKI) and chronic kidney disease (CKD).[2,3] AKI is a frequent complication in hospitalized patients, particularly during sepsis and after major surgery, and often accelerates progression to CKD, which affects more than 850 million individuals worldwide and markedly increases cardiovascular morbidity and mortality.[1]

Despite their abundance and rapid recruitment during kidney injury, neutrophils have historically received less attention in nephrology than adaptive immune cells. Classification systems for glomerulonephritis largely focus on immunoglobulin and complement deposition, while therapeutic development has predominantly targeted lymphocytes and complement pathways.[4] However, neutrophils are among the first leukocytes recruited to the injured and inflamed kidney, where they contribute to host defense but also mediate tissue injury through release of ROS, proteases, cytokines,

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and NETs. Persistent or dysregulated neutrophil activation has increasingly been implicated in thromboinflammation, endothelial injury, autoimmunity, and maladaptive repair during AKI-to-CKD transition.

Recent clinical success of complement-targeting therapies further highlights the importance of neutrophil-driven pathways in kidney disease. Iptacopan, an oral factor B inhibitor, reduces proteinuria in IgA nephropathy and C3 glomerulopathy; by suppressing C5a generation, it may also attenuate complement-mediated neutrophil activation..[5,6]

Importantly, neutrophil function in the kidney is highly context- and compartment-dependent.[7,8] The same neutrophil can mediate antimicrobial defense during pyelonephritis yet promote immunothrombosis in cholesterol crystal embolism, and necroinflammation in crystal nephropathy, ischemic AKI, or autoimmune disease. Local metabolic and inflammatory microenvironments, including hypoxia, hyperosmolarity, uremic toxins and metabolites, and cytokine exposure, shape neutrophil activation states and effector functions. Understanding how neutrophil phenotypes are regulated across kidney compartments and disease states may therefore identify therapeutic strategies that limit tissue injury while preserving antimicrobial host defense.

Neutrophils have traditionally been viewed as short-lived innate effector cells primarily involved in antimicrobial defense to infection. This review summarizes recent advances in immunology and nephrology that reveal remarkable functional plasticity of neutrophils across distinct kidney microenvironments and disease states. Their interactions with tubular epithelial cells, endothelial cells, complement pathways, platelets, macrophages, and adaptive immune cells position neutrophils at the center of kidney inflammation and repair. At the same time, emerging technologies such as single-cell sequencing, spatial transcriptomics, and intravital imaging are redefining our understanding of neutrophil heterogeneity and tissue-specific behavior in the kidney. These insights are beginning to reshape therapeutic concepts beyond broad immunosuppression toward selective modulation of pathogenic neutrophil programs.

## Neutrophil Biology and Diversity

Neutrophils are produced in the bone marrow at a rate of approximately $10^9$ cells per day in healthy adults.[10] Granulopoiesis takes about five days and is primarily regulated by granulocyte colony-stimulating factor (G-CSF). Mature neutrophils are subsequently released into the circulation, where they patrol the vasculature for inflammatory signals and have a circulating half-life of 6 to 12 hours.[8–10] In the absence of tissue recruitment, aged neutrophils undergo apoptosis and are cleared by macrophages eg in the bone marrow. During infection or sterile inflammation, homeostatic granulopoiesis is replaced by emergency granulopoiesis, which accelerates neutrophil production and mobilizes bone marrow reserves.[11] As a result, immature neutrophil populations may enter the circulation, often displaying reduced phagocytic capacity, altered chemokine receptor expression, and enhanced propensity for NET formation (Figure 1A).[9,12]

Neutrophils are essential for immediate host defense through phagocytosis, degranulation, ROS production, and NET formation.[13] However, these effector functions are not deployed uniformly. A neutrophil that phagocytoses an opsonized bacterium does not necessarily form NETs, whereas neutrophils exposed to crystals or immune complexes within the glomerulus or interstitium may undergo NETosis.[7,9,12] Which effector function predominates depends on the inflammatory context, tissue compartment, and activation state in eg AKI, CKD, and AAV.[8]

A central concept in neutrophil biology is the distinction between priming and activation. Resting neutrophils exposed to low-grade inflammatory stimuli such as tumor necrosis factor-α (TNF-α), granulocyte-macrophage colony-stimulating factor (GM-CSF), type I interferons, or subactivating concentrations of C5a become primed for exaggerated responses to subsequent stimulus.[9,14,15] Priming increases surface expression of adhesion and Fc receptors, mobilizes granule proteins such as myeloperoxidase (MPO) and proteinase 3 (PR3) to the plasma membrane, promotes assembly of NADPH oxidase complexes and lowers the threshold for NET formation. Many neutrophils in autoimmune and complement-mediated kidney diseases are thought to exist in a primed rather than fully activated state. Clinically, disease activity therefore correlates less with absolute neutrophil counts than with markers of activation and priming, including MPO, soluble CD62L, and surface CD11b.[16,17] This concept also provides a therapeutic rationale for targeting upstream activation pathways rather than broadly suppressing neutrophils.

Neutrophil granules provide the molecular machinery for their effector functions. Azurophilic granules contain MPO, neutrophil elastase, cathepsin G, defensins, and PR3, whereas specific and gelatinase granules contain lactoferrin, lysozyme, and matrix metalloproteinases. During priming, MPO and PR3 translocate to the cell surface, where they

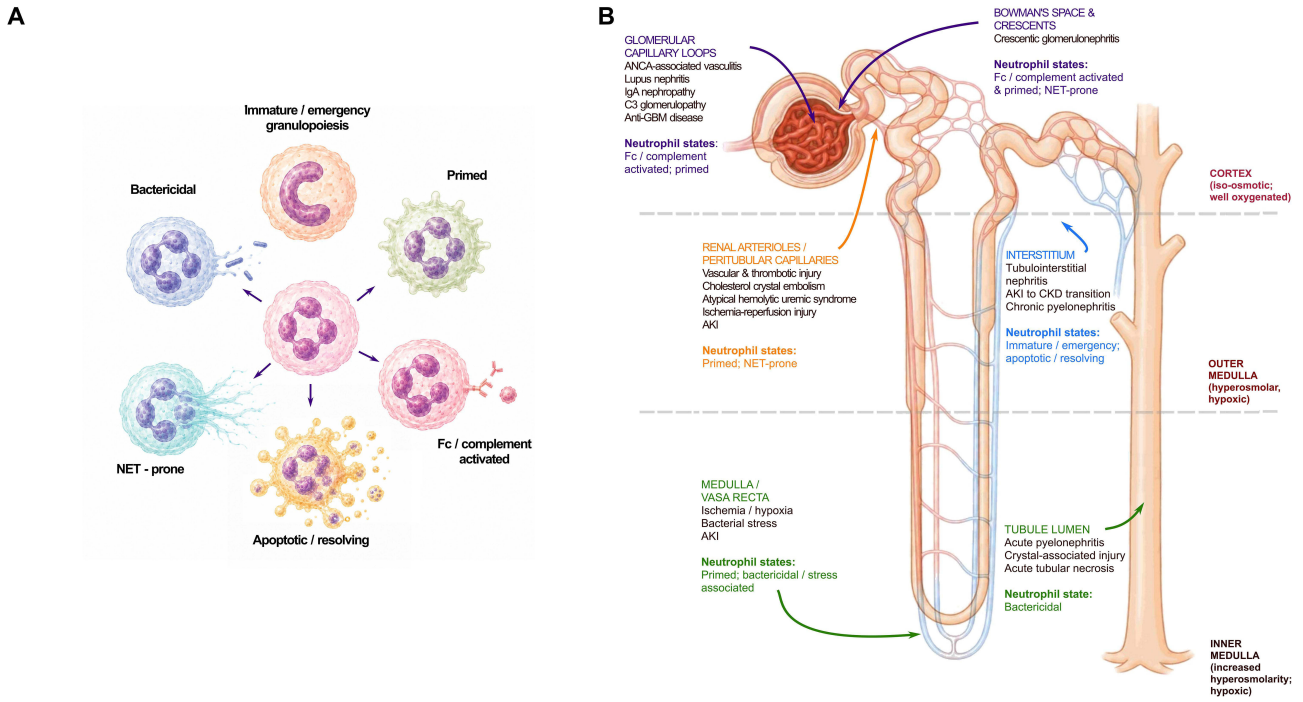


**Figure 1** Renal compartments shape neutrophil state in kidney injury. (**A**) Neutrophils occupy a continuum of functional states. A circulating neutrophil can be biased toward any of these programs by the signals it encounters. (**B**) The kidney provides anatomically distinct microenvironments that imprint the states defined in A, each compartment shown with its representative diseases and dominant neutrophil states alongside the cortex to medulla gradient. Arrows connect each compartment to its label and indicate microenvironmental imprinting of neutrophil state. Figure 1 was generated using an artificial intelligence tool, OpenAI ChatGPT (version 5.5), image generation feature, and was then edited and labeled by the authors.

become accessible to circulating autoantibodies in AAV.[14,18] NETs, consisting of decondensed chromatin decorated with granule proteins, were first described as antimicrobial structures,[11] but are now recognized as important mediators of sterile inflammation and autoimmunity.[12,19–21] NET-associated histones generated by peptidylarginine deiminase 4 (PAD4), MPO, and PR3 are directly tissue-damaging and immunogenic,[22] while extracellular DNA and chromatin activate nucleic acid sensing pathways, including toll-like receptor 9 (TLR9) and cGAS-STING. In lupus nephritis, these pathways reinforce type I interferon responses and perpetuate autoimmunity.

Recent studies have further highlighted substantial neutrophil heterogeneity across inflammatory disease. Low-density granulocytes (LDGs), which co-separate with peripheral blood mononuclear cells during density-gradient centrifugation, are enriched in systemic lupus erythematosus (SLE) and can also be detected in AAV.[23,24] LDGs exhibit increased spontaneous NET formation and enhanced type I interferon signaling,[23,24] and their NETs are enriched in oxidized mitochondrial DNA capable of amplifying interferon responses in lupus nephritis.[25] In parallel, aged neutrophils characterized by increased C-X-C motif chemokine receptor 4 (CXCR4) and reduced CXCR2 expression display altered trafficking and effector behavior during chronic inflammation.[26–28]

Importantly, these descriptors define overlapping functional states rather than fixed neutrophil lineages.[8,29] A neutrophil may simultaneously exhibit features of aging, priming, NET susceptibility, or emergency granulopoiesis depending on the inflammatory milieu. Within the kidney, local factors including hypoxia, hyperosmolarity, complement activation, immune complexes, endothelial injury, and uremic metabolites further shape neutrophil phenotype and function. This context-dependent plasticity is increasingly recognized as a central determinant of neutrophil-mediated kidney injury.

## The Kidney as a Regulator of Neutrophil Behavior

Neutrophils rapidly accumulate in the kidney during AKI, both in experimental models and in human biopsies, particularly following ischemia–reperfusion injury (IRI).[30] Within minutes after reperfusion, neutrophils adhere to activated endothelial cells and platelets, contributing to capillary plugging, vascular congestion, and impaired


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microvascular perfusion.[30] In the kidney interstitium, neutrophils amplify tissue injury and inflammation through degranulation, cytokine release, NETosis, and ROS production.[30] Consistently, blocking neutrophil recruitment using anti-ICAM antibodies or ICAM deficiency attenuates kidney injury in murine IRI models.[31,32]

Sterile tissue injury itself further promotes neutrophil activation. Damage-associated molecular patterns (DAMPs) released during IRI, including histones and mitochondrial components, can directly trigger NET formation.[33] NETs subsequently amplify oxidative stress and histone release, thereby promoting tubular epithelial cell death and necroinflammation.[33] Recent experimental studies suggest that targeting NET formation may represent a therapeutic strategy in AKI. For example, pharmacological inhibition of PAD4, a key regulator of NETosis, reduces tubular apoptosis and pyroptosis in contrast-induced AKI.[34,35] Importantly, the kidney is not merely a passive target of neutrophil-mediated injury but actively shapes neutrophil behavior through its unique anatomical and metabolic microenvironment. Distinct kidney compartments expose infiltrating neutrophils to different combinations of shear stress, osmolarity, hypoxia, endothelial activation, immune complexes, complement activation, and tissue-derived metabolites; thereby biasing neutrophil effector programs toward antimicrobial defense, thromboinflammation, NET formation, or maladaptive tissue remodelling. Figure 1B summarizes kidney compartments that imprint compartment-specific neutrophil states and highlights representative disease contexts associated with each microenvironment.

## Renal Arterioles

Renal arterioles represent a vascular niche in which circulating neutrophils encounter endothelial injury, platelet activation, and high shear stress.[36] These conditions favor leukocyte adhesion, β2-integrin activation, and platelet-neutrophil interactions that promote immunothrombosis. In cholesterol crystal embolism, cholesterol crystals released from atherosclerotic plaques lodge within small renal arteries and arterioles, where they induce endothelial injury, thrombotic microangiopathy, inflammasome activation, and necroinflammation.[37–40] In this setting, infiltrating neutrophils acquire a highly proinflammatory and prothrombotic phenotype characterized by β2-integrin activation, NET formation, oxidative burst, and GSDMD-dependent pyroptosis.[40,41]

## Glomerular Capillaries and Bowman's Space

The glomerulus functions as a specialized filtration network in which its fenestrated capillaries create conditions that favor the trapping of neutrophils during inflammation.[42] Unlike post-capillary venules, where leukocyte recruitment depends on P-selectin rolling followed by integrin-dependent adhesion, the glomerular circulation supports a distinct mechanism in which neutrophil arrest occurs largely independent of selectins and relies instead on integrin interactions, particularly MAC-1,[43] often facilitated by platelet-mediated bridging.[43] Once retained within capillary beds, neutrophils are exposed to circulating autoantibodies, immune complexes, and complement fragments, which drive strong activation through Fcγ and complement receptors.[14] This environment promotes robust effector responses, including degranulation and NET formation,[14] making neutrophils key contributors to glomerular injury in diseases such as AAV, lupus nephritis, immunoglobulin A (IgA) nephropathy, C3 glomerulopathy, and anti-glomerular basement membrane (GBM) disease.

In more severe forms of glomerular injury, particularly rapidly progressive or crescentic glomerulonephritis, damage to the glomerular basement membrane allows inflammatory mediators, coagulation factors, and plasma proteins to enter Bowman's space. This transforms the normally protective urinary space into a procoagulant and proinflammatory niche.[44,45] Consequently, parietal epithelial cells lining Bowman's capsule become activated and together with recruited monocytes/macrophages form cellular crescents, which compress the glomerular tuft and disrupt filtration.[45,46] Neutrophils play their most important role early in this process, amplifying endothelial injury and promoting capillary wall rupture through degranulation, NET release, and inflammatory signals.[14,47] In this way, they act as upstream effectors of necrotizing glomerular injury in diseases that overlap with the glomerular compartment, including AAV, anti-GBM disease, severe lupus nephritis, and crescentic forms of IgA nephropathy.

## Peritubular Capillaries

Peritubular capillaries constitute the post-glomerular microvascular network that surrounds the tubules and supplies oxygen and nutrients to highly metabolically active tubular epithelial cells. Unlike upstream arterioles, where flow

limitation can be driven by discrete thromboinflammatory occlusion, this downstream exchange bed is particularly sensitive to subtle or heterogeneous reductions in perfusion. Even modest disturbances in capillary flow can therefore translate into rapid impairment of oxygen delivery to adjacent tubular segments. Consistent with this vulnerability, intravital imaging has shown that peritubular capillary dysfunction may arise before detectable changes in conventional biomarkers of kidney injury, underscoring the importance of microvascular perfusion as an early determinant of AKI.[48]

During kidney injury, peritubular capillary flow can be compromised without a single focal obstruction. Multiple overlapping mechanisms contribute, including endothelial swelling, leukocyte adhesion, platelet aggregation, erythrocyte congestion, pericyte-mediated capillary constriction, and NET-associated endothelial injury.[34,49–51] In this context, neutrophils contribute less through classical high-shear vascular recruitment and more through their role in promoting capillary congestion, endothelial damage, and local perfusion failure.[34,36,48–51] NET formation has been observed within both glomerular and peritubular capillary compartments in experimental models of AKI, and strategies that inhibit or degrade NETs have been associated with reduced endothelial injury and improved kidney functional outcomes.[34,52] Accordingly, peritubular capillary dysfunction represents a convergent pathway rather than a disease-specific lesion, occurring in settings such as IRI, vascular forms of AKI, thrombotic microangiopathies, and cholesterol crystal embolism.[34,49,53–56]

## The Outer Medulla

The outer medulla is characterized by inherently low oxygen availability due to countercurrent oxygen exchange within the vasa recta combined with high metabolic demands of local tubular segments, especially the proximal straight tubule and thick ascending limb.[1,49] This baseline hypoxic state renders the region particularly vulnerable to ischemic and toxic injury. Within this environment, hypoxia-driven stabilization of HIF-1α may influence infiltrating neutrophils by promoting glycolytic metabolism and prolonging neutrophil survival, potentially contributing to sustained inflammatory activity, although direct in vivo confirmation remains limited.[57,58] As a result, this compartment is especially relevant to forms of AKI involving secondary neutrophil recruitment and NET formation, such as IRI, toxin-induced AKI, and sepsis-associated AKI.[53,54]

## The Interstitium

The interstitium represents a compartment where a failure to resolve inflammation becomes central to persistent or chronic inflammation. Following acute injury or repeated insults, maladaptive tubular adaptation, sustained transforming growth factor beta (TGF-β) signaling, persistent macrophage accumulation, and fibroblast activation converge to drive extracellular matrix deposition and interstitial fibrosis.[59–61] Neutrophils can exacerbate this process when their clearance is inefficient and cellular recruitment persists,[62,63] as uncleared apoptotic neutrophils may undergo secondary necrosis, releasing DAMPs, proteases, histones, and NET components that perpetuate macrophage activation and ongoing tissue injury.[52,63,64] Over time, this creates a self-sustaining inflammatory-fibrotic loop underlying conditions such as AKI-to-CKD transition, chronic pyelonephritis, chronic interstitial nephritis, and chronic allograft injury with interstitial fibrosis and tubular atrophy.[59,65]

## Tubule Lumen

The tubular lumen is characterized by direct exposure to urinary contents rather than blood or tissue fluid, making it uniquely vulnerable to injury from precipitated or accumulated intraluminal material. In diseases such as myeloma cast nephropathy, nephrocalcinosis, and chronic uric acid nephropathy, light chains, crystals, or urate deposits accumulate within the tubular lumen, leading to tubular injury and obstruction of tubular flow.[40,66,67] In these conditions, the primary insult originates from luminal crystalline material itself, while neutrophils are recruited secondary in response to epithelial stress and danger signals, where they may further amplify injury in the surrounding interstitium.

In infectious settings such as pyelonephritis and sepsis, the role of the tubular lumen is distinct. Ascending bacteria enter the urinary tract,[68] and tubular epithelial cells respond by producing chemokines that drive neutrophil migration across the epithelium into the lumen, resulting in pyuria.[69] Here, neutrophil infiltration serves a protective function, contributing to bacterial clearance rather than primarily reflecting sterile crystal- or cast-mediated injury.

## Osmotic and Metabolic Milieu

Beyond its anatomic compartments, the kidney exposes neutrophils to a highly dynamic biochemical environment defined by gradients in oxygen tension, osmolarity, metabolites, and retained solutes. The osmotic gradient is particularly important because the cortex remains relatively close to normal extracellular osmolarity, whereas the medulla becomes progressively hyperosmolar due to NaCl and urea handling during urinary concentration.[1,70] Consequently, neutrophils entering the medulla encounter simultaneous hypoxic and osmotic stress. Cellular adaptation to hypertonicity is largely regulated by the transcription factor NFAT5/TonEBP, which is essential for medullary homeostasis[71] and also participates in immune regulation in macrophages and T cells. However, whether NFAT5 directly programs neutrophil responses within the medulla remains unclear.[72]

The effects of hyperosmolarity on neutrophils are complex and appear to depend on both exposure time and the surrounding inflammatory environment. Short-term exposure to hypertonic NaCl can suppress NOX2-dependent NET formation and ROS production, whereas prolonged exposure to high salt may instead promote delayed neutrophil activation.[73,74] Thus, the medullary osmotic gradient is best understood as a modulatory microenvironment able to shape neutrophil survival, chemokine responses, ROS production, and NET release rather than acting as a single inflammatory signal.

Metabolic factors provide an additional layer of regulation. Activated neutrophils rely strongly on glycolysis, while the pentose phosphate pathway supplies reducing equivalents necessary for NADPH oxidase activity. Glucose, and in some contexts glutamine, also contribute to NET formation.[75] Within the kidney, these metabolic programs are particularly relevant in the outer medulla, where hypoxia and HIF-1α stabilization support glycolytic adaptation and prolong neutrophil survival.[57] During ischemic stress, succinate can accumulate and function as a potential priming signal through SUCNR1/GPR91 signaling, although definitive in vivo evidence in kidney neutrophils remains limited.[76,77]

In CKD, the metabolic environment becomes further altered by the retention of uremic toxins/solutes and immunomodulatory mediators that contribute to chronic inflammation and immune dysfunction. Patients with advanced kidney disease, especially those on dialysis, exhibit increased susceptibility to infection and impaired vaccine responses due to the secondary immunodeficiency related to kidney disease (SIDKD).[78] Uremic solutes/metabolites and immunoregulatory proteins, including indoxyl sulfate, p-cresyl sulfate, leptin, and fibroblast growth factor 23, have been implicated in dysregulated neutrophil function.[78–81] Neutrophil dysfunctions include impaired phagocytosis, reduced respiratory burst, altered migration,[82,83] and diminished NET release and NETosis.[84] Mechanistically, these solutes act on distinct neutrophil effector arms rather than as nonspecific toxins. Indoxyl sulfate and p-cresyl sulfate, which are bound to protein and poorly cleared by conventional dialysis, raise basal ROS production and accelerate apoptosis while blunting the stimulated respiratory burst, chemotaxis, and bacterial killing.[80,85] FGF23 acts directly on neutrophils to suppress the activation of the β2 integrin CD11b/CD18 by chemokines and its downstream signaling, and thereby reduces firm adhesion, transendothelial migration, and recruitment to infected tissue.[81] In addition, soluble uric acid, which commonly accumulates in CKD-associated asymptomatic hyperuricemia, has been shown to impair β2 integrin activation and internalization/recycling, thereby altering neutrophil migration during sterile inflammation.[86] At the same time, soluble uric acid drives hyperinflammation, characterized by increased cytokine levels, neutrophil activation and recruitment, while simultaneously impairs host defense in sepsis by suppressing neutrophil effector functions including phagocytosis, bacterial killing, and ROS generation.[87] This suggests that soluble uric acid may compromise immune competence during infection. The net result is a maladaptive state in which diminished pathogen clearance coexists with persistent low-grade activation, linking uremic retention to both the infection susceptibility and the persistent inflammation that characterize SIDKD.[78] Most evidence derives from in vitro exposure and murine models, and the relative contribution of individual solutes to intrarenal neutrophil function in patients remains to be defined.

Together, these observations emphasize that neutrophils entering different kidney compartments are exposed to distinct factors of oxygen availability, osmotic stress, metabolic substrates, retained solutes, and inflammatory mediators. As a result, neutrophil survival, activation state, migration, and effector function are continuously shaped by the unique microenvironment encountered across the kidney.

## Therapeutic Settings

The disease contexts below can be organized into four therapeutic settings according to the dominant neutrophil state and the most appropriate therapeutic targets: (1) conditions in which neutrophil antimicrobial function must be preserved; (2) conditions in which neutrophils drive microvascular immunothrombosis; (3) conditions in which upstream immune signals pathologically activate neutrophils; and (4) conditions characterized by impaired clearance and failed resolution of neutrophilic inflammation. This framework emphasizes that neutrophils do not play a uniform role across kidney diseases and that effective intervention depends on identifying the dominant pathogenic mechanisms within a given disease.

### Setting 1. Conditions in Which Neutrophil Function Must Be Preserved

In acute and chronic infections, neutrophils are important components of host defense, making preservation of their antimicrobial function a therapeutic priority. In acute pyelonephritis, ascending urinary tract infection, and urosepsis, intact neutrophil recruitment, migration, and activation are required for bacterial clearance. The therapeutic challenge is therefore not suppression of neutrophils themselves, but limiting of the collateral tissue injury caused by excessive ROS production, degranulation, and NET formation, while maintaining effective pathogen killing.[53,54]

A major limitation of neutrophil-mediated bacterial clearance is that pathogens are not always freely accessible within the urinary tract. Uropathogenic *E. coli* can invade epithelial cells, form intracellular bacterial communities, adopt filamentous morphologies, or persist in biofilm-like niches; thereby evading extracellular immune defenses. Consequently, even robust neutrophil recruitment may be insufficient when bacteria reside within protected epithelial or catheter-associated compartments.[88,89]

This balance becomes particularly apparent in sepsis-associated AKI, where neutrophils remain essential for antimicrobial defense but NET formation can simultaneously worsen peritubular capillary occlusion and amplify tubular necrosis.[53,54,90] Therapeutic strategies therefore aim to selectively reduce NET-mediated injury while preserving phagocytic capacity. Approaches targeting downstream NET components, such as GSDMD or PAD4, are conceptually attractive because they interfere with NET formation without broadly suppressing upstream neutrophil activation. DNase I-mediated degradation of extracellular NETs has shown benefit in experimental sepsis models,[91] although translation into clinical practice remains unclear.

Chronic infectious conditions, including reflux-associated pyelonephritis, obstructive nephropathy, schistosomiasis-associated kidney disease, and infection-associated immune complex glomerulonephritis, represent a distinct challenge characterized by persistent but incomplete bacterial clearance. In other cases, incomplete clearance stems not from an anatomical obstacle or the organism itself but from a primary immunodeficiency, whether in the neutrophils or in other components of host defense. In either setting, sustained neutrophil recruitment drives interstitial injury and progressive fibrosis; when the neutrophils themselves function normally, the damage reflects the persistence of this response rather than any failure of microbial killing. Accordingly, antimicrobial therapy with antibiotics and restoration of urinary drainage remain the primary interventions, whereas broad anti-inflammatory suppression risks worsening uncontrolled infection.

### Setting 2. Conditions in Which Neutrophils Drive Microvascular Injury

In IRI, the microvascular component of sepsis-associated AKI, cholesterol crystal embolism, and thrombotic microangiopathies, neutrophils contribute primarily through immunothrombosis, the pathological convergence of innate immune activation and coagulation within the microvascular lumen.[58] DAMPs released by necrotic tubular cells activate complement pathways and Toll-like receptors in recruited neutrophils, promoting degranulation and NET formation that propagate vascular occlusion and extend ischemic injury.

IRI represents one of the most common causes of intrinsic AKI in hospitalized patients and is central to delayed graft function after kidney transplantation.[49] Ischemic injury induces ATP depletion, mitochondrial permeability transition cell death, and tubular necrosis, while reperfusion-associated succinate accumulation generates bursts of mitochondrial ROS that promote neutrophil activation.[76] NET-derived histones further amplify tissue injury and may contribute to organ failure.[52] Experimental studies have demonstrated protective effects from blocking complement C5a or its receptor

(C5aR1/CD88), GSDMD, and PAD4 leading to reduced neutrophil-mediated IRI, although no neutrophil-targeted therapy has yet completed a successful Phase III trial for IRI-associated AKI.

Cholesterol crystal embolism provides a clinically relevant AKI model sterile immunothrombosis.[38] Cholesterol crystals formed in small renal arteries trigger complement activation, coagulation and recruit neutrophils that release NETs and GSDMD-dependent inflammatory signals.[39–41] Pharmacological inhibition of C5aR1 and GSDMD attenuates crystal-induced immunothrombosis in mouse models, and circadian variation in neutrophil aging appears to influence injury severity.[37,41,56] Despite strong mechanistic data, anti-complement approaches have not been validated in randomized clinical trials.

Atypical hemolytic uremic syndrome (aHUS) occupies the intersection of complement-driven thrombotic microangiopathy (TMA) and sterile necroinflammation. Dysregulated activation of the alternative complement pathway, whether caused by mutations in complement regulatory proteins or autoantibodies against factor H, leads to persistent endothelial deposition of C3b and C5a. These signals recruit and activate neutrophils, amplifying platelet-rich microvascular thrombosis.[92] In this setting, complement blockade with the anti-C5 monoclonal antibodies eculizumab and ravulizumab has become standard therapy by interrupting the upstream complement signal responsible for neutrophil activation and endothelial injury.[93]

Shiga toxin-producing *E. coli*-associated hemolytic uremic syndrome (STEC-HUS) is an infection-initiated TMA in which Shiga toxin induces endothelial injury, complement activation, and platelet aggregation. Neutrophils amplify vascular thrombosis through NET release and MPO-mediated oxidative stress.[55] Although eculizumab is used off-label in severe STEC-HUS, the specific contribution of complement blockade to neutrophil-driven pathology remains incompletely defined. Although NETs contribute to microvascular injury across these disorders, the disease differ in their triggers. In IRI, NETs intensify hypoxia-associated no-reflow injury; in cholesterol crystal embolism, they propagate crystal-driven immunothrombosis; in aHUS, they amplify complement-saturated endothelial injury; and in STEC-HUS, they follow an infection-triggered toxin injury. These differences suggest that effective therapy will likely require disease-specific therapeutic approaches rather than a single generalized anti-NET therapy.

## Setting 3. Conditions in Which Upstream Signals Activate Neutrophils

In AAV, anti-GBM disease, lupus nephritis, IgA nephropathy, and C3 glomerulopathy, neutrophils become pathogenic primarily because they are exposed to antibodies or complement factors. In these diseases, therapeutic strategies preferentially target the initiating immune pathways rather than globally suppressing neutrophil function.

AAV provides the clearest example of this paradigm. Circulating neutrophils are not intrinsically pathogenic during disease remission but become activated after priming by cytokines such as TNF-α and IL-17, which translocate MPO and PR3 to the neutrophil surface where they become targets for ANCA binding.[14,15] Locally generated C5a further amplifies neutrophil priming through C5aR1 signaling.[94]

Anti-GBM disease similarly involves antibody-mediated injury amplified by recruited neutrophils.[95] Autoantibodies directed against the α3 chain of type IV collagen bind the glomerular basement membrane, activate complement, and recruit neutrophils that release elastase and MPO, thereby worsening basement membrane disruption and crescent formation. However, because the initiating pathology remains antibody driven, plasma exchange and immunosuppression remain the therapeutic priorities rather than direct neutrophil-targeted interventions.

In lupus nephritis, immune complex deposition and complement activation generate C5a and inflammatory signals that recruit and prime neutrophils.[96] LDGs in SLE are prone to spontaneous NET formation, and their NETs contain oxidized mitochondrial DNA that activates plasmacytoid dendritic cells to produce type I interferons.[97] Therapeutic agents such as voclosporin, a calcineurin inhibitor, and belimumab, which neutralizes BAFF, target mechanisms upstream to immune complex formation rather than neutrophils directly.[98,99]

Post-infectious glomerulonephritis, including post-streptococcal GN, is characterized by complement-dependent glomerular neutrophil infiltration and endocapillary proliferation during the acute phase. In most pediatric patients, the disease is transient and followed by spontaneous resolution, whereas adults are more likely to experience incomplete recovery and progression toward CKD.

In IgA nephropathy, galactose-deficient IgA1 (Gd-IgA1) immune complexes deposit in the mesangium and activate the alternative complement pathway. Although neutrophils are not the dominant inflammatory infiltrate in most cases, complement-driven C5a recruits and primes circulating neutrophils during active disease flares, contributing to

proteinuria and hematuria. This is therapeutically supported by factor B inhibitor with iptacopan, which reduces alternative complement pathway amplification and has demonstrated reductions in proteinuria by more than 38% in the APPLAUSE-IgAN trial. Final 24-month data confirmed durable benefit, establishing the alternative complement pathway as the primary therapeutic target in IgA nephropathy.[5,100]

C3 glomerulopathy arises from dysregulated alternative complement pathway activation caused by autoantibodies against C3 convertase or mutations in complement regulators, producing persistent glomerular C3 deposition.[101] Neutrophils recruited to complement-deposited glomeruli amplify filtration barrier injury through degranulation and inflammatory signaling. Early clinical studies evaluating iptacopan in C3 glomerulopathy suggest therapeutic efficacy consistent with its mechanism in IgA nephropathy.

Across these diseases, antibody and complement pathways represent preferred therapeutic targets because they lie upstream of neutrophil adhesion, priming, degranulation, and NET formation. Blocking these initiating signals may therefore attenuate kidney inflammation while preserving systemic antimicrobial host defense.

## Setting 4. Disease States in Which Neutrophil Clearance Is Impaired

In the transition from AKI-to-CKD and in chronic fibrosing nephropathies, neutrophils are less often driven by acute hyperactivation than by defective resolution of inflammation. In advanced CKD, uremic toxins/solutes and metabolites impair neutrophil function, contributing to SIDKD,[78] in which impaired host defense coexists with persistent inflammation as well as a shift in the secretome of the intestinal microbiota and barrier dysfunction.

Resolution of inflammation is an active and tightly regulated process.[102] Under physiological conditions, tissue-infiltrating neutrophils undergo apoptosis within 24 to 48 hours and are subsequently cleared by macrophages through efferocytosis mediated by receptors such as MerTK and TAM.[63] Successful clearance promotes macrophage transition toward anti-inflammatory and tissue-repair phenotypes. Failure of this, whether due to impaired neutrophil apoptosis, defective efferocytosis, or insufficient production of pro-resolving mediators, perpetuates inflammation and promotes AKI-to-CKD transition.[62,102] Patients who recover from an AKI episode retain an elevated risk for CKD even after creatinine normalization.[63] Failed efferocytosis of apoptotic neutrophils may trigger DAMP release, contributing to macrophage activation and TGF-β-driven fibroblast differentiation. Pro-resolving mediators including lipoxins, resolvins, protectins, and maresins, can limit neutrophil recruitment and promote efferocytosis but their biosynthesis may be impaired in uremia.[102]

As kidney function declines, accumulation of uremic toxins/solutes and metabolites increases leading to neutrophil dysfunction,[79,80] thereby contributing to SIDKD. Recent evidence suggests that soluble uric acid acts as an immunometabolic regulator able to promote hyperinflammation while simultaneously impairing host defense during bacterial infection.[87] Urate-lowering therapy with febuxostat partially restored neutrophil-mediated host defense,[87] supporting the concept that correction of CKD-associated metabolic disturbances may improve immune competence in kidney disease. Similarly, neutralization of FGF23 restored neutrophil recruitment and host defense in mice with CKD,[81] although clinical validation remains necessary.

Emerging studies from other chronic neutrophil-driven inflammatory diseases further support the therapeutic relevance of modulating maladaptive neutrophil programs. In bronchiectasis, inhibition of dipeptidyl peptidase-1 (DPP-1), a regulator of neutrophil serine protease activation, reduced disease exacerbations in a phase III clinical trial of brensocatib,[103] and recent reviews have highlighted DPP-1 inhibition as a broader strategy for controlling chronic neutrophil-mediated tissue injury without complete neutrophil depletion.[104] These findings reinforce the concept that selectively modulating neutrophil effector pathways, rather than globally suppressing neutrophils, may also hold therapeutic potential in kidney disease.

The neutrophil effector functions targeted for their pathogenic potential are the same functions required for host defense, so long term inhibition risks impairing antimicrobial competence. This concern is greatest in CKD, where SIDKD already compromises neutrophil function.[78] The risk profile is, however, specific to the mechanism, which reinforces the rationale for selective rather than global suppression. By contrast, terminal complement blockade with eculizumab or ravulizumab markedly increases susceptibility to encapsulated organisms, particularly Neisseria meningitidis, mandating meningococcal vaccination and often antibiotic prophylaxis, and vaccination is incompletely

protective.[105] Agents acting on shared distal effectors carry broader theoretical risk. PAD4 and GSDMD are required for antimicrobial defense that depends on NETs and pyroptosis, so their inhibition could impair pathogen containment, and degradation of NETs by DNase does not discriminate protective from pathogenic NETs. Clinical safety data for these strategies in kidney disease are not yet available. The DPP-1 (cathepsin C) inhibitor brensocatib, which lowers maturation of neutrophil serine proteases, was generally tolerated in bronchiectasis, with hyperkeratosis at higher doses and without a clear excess of serious infection, but has not been evaluated in kidney disease.[103,104] These considerations argue for selectively blocking a defined pathogenic program while sparing phagocytosis and oxidative killing, and for incorporating infection surveillance into any future kidney trial.

Glomerulosclerosis, including diabetes with CKD, polycystic kidney disease, chronic allograft injury, or CKDu/CKDx, are associated with persistent low-grade interstitial inflammation in which neutrophil-derived proteases contribute to tubular injury and fibrosis. However, neutrophils function primarily as secondary amplifiers rather than initiating drivers of disease, making interventions directed at upstream metabolic, hemodynamic, or fibrotic pathways more likely to alter disease progression than direct neutrophil-targeted strategies.

Consistent with this view, the two drug classes that have most reshaped CKD therapy, sodium-glucose cotransporter-2 (SGLT2) inhibitors, now established for cardiorenal protection in both diabetic and nondiabetic CKD, and glucagon-like peptide-1 receptor agonists (GLP-1 RA), established for cardiorenal protection in type 2 diabetes with CKD, with evidence in nondiabetic CKD still emerging, exert anti-inflammatory effects that may indirectly restrain neutrophilic injury. SGLT2 inhibitors reduce oxidative stress, endothelial dysfunction, and inflammasome associated signaling, pathways that also contribute to the necroinflammation associated with crystals and ischemia that neutrophils help propagate,[106] and GLP-1 RA likewise attenuate renal inflammation and immune cell accumulation alongside their hemodynamic and metabolic actions.[107] Both classes are relevant in diabetic kidney disease, where NET formation is increasingly implicated in progression.[108] Whether these anti-inflammatory effects directly reprogram intrarenal neutrophil states or are secondary to improved metabolic and hemodynamic control remains to be established, but they illustrate how upstream metabolic intervention may modulate the neutrophilic microenvironment without impairing host defense.

## Translational Outlook

Current kidney disease classifications are based mainly on histology and clinical presentation, but these do not necessarily identify neutrophils driving injury in an individual patient. Two patients with the same diagnosis may have very different inflammatory states: one may show strong complement-mediated neutrophil priming and NET formation, whereas another may have predominantly fibrotic or poorly resolving inflammation. As a result, stratifying patients according to neutrophil state rather than disease alone may improve both therapeutic selection and prediction of treatment response.

This approach depends on biomarkers that capture specific neutrophil activation states. Several candidate biomarkers are currently under investigation. Activated CD11b, detected using conformation-specific antibodies to the high-affinity I-domain (CBRM1/5 epitope), reflects neutrophil priming and adhesion ability in the blood.[2] Soluble L-selectin (CD62L), which is shed during neutrophil activation, provides a complementary plasma-based indicator of systemic neutrophil activation. NET-associated markers, including MPO-DNA complexes, citrullinated histone H3, and cell-free DNA, can be detected in blood and urine and correlate with AKI severity in IRI and AAV.[9,15] In complement-mediated diseases, circulating fragments such as Bb, sC5b-9, and C5a may quantify the upstream inflammatory signals responsible for neutrophil recruitment and activation. The clinical validation of these candidates, however, remains preliminary, and none has been qualified as a validated diagnostic. Each carries limitations of specificity. Activated CD11b (CBRM1/5) and shed CD62L reflect leukocyte activation broadly, because these epitopes are also expressed or released by monocytes and lymphocytes, while cell-free DNA is released by many forms of regulated and necrotic cell death and is therefore the least specific to NETs. MPO-DNA complexes are more selective for neutrophil origin but lack assay standardization and harmonized reference ranges, and even citrullinated histone H3, the most restricted to NETs of the three, remains sensitive to sample handling and antibody choice.[109] Reported associations derive largely from small, single center, cross sectional cohorts that use nonstandardized assays without prospectively defined sensitivity and specificity and without validation against kidney histology. Circulating NET surrogates have not consistently discriminated active disease from remission even in ANCA-associated vasculitis,[110] and to date only an activated β2 integrin (LFA-1) readout has been

advanced as a candidate mechanistic biomarker with formal validation analyses in that setting.[17] These candidates are accordingly best regarded as exploratory pharmacodynamic and stratification markers whose diagnostic and prognostic performance for intrarenal neutrophil activity must be established in adequately powered prospective studies anchored to biopsy before they can guide patient stratification by neutrophil state.

Recent studies also suggest that broader neutrophil developmental states may have prognostic value. For example, a recent study demonstrated that maladaptive emergency granulopoiesis, characterized by expansion of immature circulating neutrophils, was associated with poor outcomes in patients with decompensated liver cirrhosis,[111] highlighting how systemic neutrophil-state and -phenotype profiling may identify pathologic inflammatory responses linked to organ injury and immune dysfunction. Although performed outside the kidney field, this work illustrates how transcriptional and phenotypic characterization of neutrophil states could eventually be applied to kidney diseases to distinguish patients with predominant immunothrombotic, hyperinflammatory, or dysfunctional neutrophil responses.

In parallel with circulating biomarkers, tissue-based approaches are increasingly being used to define neutrophil states directly within the kidney. Immunohistochemistry and immunofluorescence can identify neutrophil accumulation and NET deposition in human biopsy samples using markers such as citrullinated histone 3 and MPO. More advanced transcriptomic approaches, including single-nucleus and single-cell RNA-sequencing, provide insight into neutrophil activation pathways within injured tissue, although technical limitations remain because neutrophils contain relatively low RNA content and high nuclease activity. Spatial transcriptomics may help overcome some of these challenges by preserving tissue architecture while simultaneously mapping inflammatory gene expression across distinct kidney compartments. Table 1 summarizes where kidney-based proteomic, single-cell or single-nucleus RNA-sequencing, and spatial or imaging evidence exists, and where neutrophil-state biology remains insufficiently resolved. In Table 1, we further rank each gap by research priority, reflecting the strength of evidence for a mechanism driven by neutrophils, the availability of a tractable neutrophil target, and disease burden.

Together, these approaches support a transition toward mechanism-based classification of kidney inflammation. Rather than treating all patients with the same histologic diagnosis identically, future strategies may identify whether complement activation, NET-driven microvascular injury, persistent neutrophil priming, maladaptive emergency granulopoiesis, or defective inflammatory resolution is the dominant process in a given patient, thereby allowing therapies to be matched more precisely to the underlying neutrophil state. Stratifying patients by activated CD11b, NET marker levels, or complement fragment concentrations could enrich trials for those most likely to respond to C5aR1 antagonism, GSDMD inhibition, or complement inhibition. Early mechanistic endpoints, such as a fall in citrullinated histone H3 or MPO-DNA, could provide pharmacodynamic evidence of target engagement before kidney outcomes become measurable.

## Conclusions

Neutrophils contribute to a broad spectrum of acute and chronic kidney diseases, but their role is highly context dependent and ranges from pathogenic effector to secondary inflammatory amplifier. The same neutrophil capable of driving immunothrombotic microvascular injury in cholesterol crystal embolism or IRI is also essential for bacterial clearance in pyelonephritis and urosepsis. What determines these divergent functions is not the neutrophil itself, but the local inflammatory, metabolic, and vascular environment within the kidney. Defining kidney inflammation according to neutrophil state may more accurately capture disease biology than classification by histologic diagnosis alone.

Recent therapeutic advances support this concept. Iptacopan targets factor B within the alternative complement pathway in IgA nephropathy and C3 glomerulopathy, limiting complement-mediated neutrophil recruitment and activation at an upstream level. This strategy targets inflammatory circuits linked to neutrophil activation without directly eliminating neutrophils themselves.

Extending this approach to conditions such as IRI, STEC-HUS, thrombotic microangiopathies, and the AKI-to-CKD transition will require improved methods to define neutrophil state in vivo. Progress will likely depend on the integration of circulating biomarkers, tissue-based imaging, spatial transcriptomics, and translational models that more faithfully reproduce the compartment-specific environments encountered within the human kidney. Ultimately, a neutrophil state–based approach may enable more precise and mechanistically guided therapies that match intervention strategies to patients.


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**Table 1** Evidence Gaps for Kidney Neutrophil-State Biology Across Kidney Diseases

| Disease Context | Renal Compartments | Proteomics/Functional Evidence | scRNA-seq/snRNA-seq Neutrophil Capture | Spatial or Imaging Evidence | Main Unresolved Gap/Next Experiment | Research Priority |
|---|---|---|---|---|---|---|
| **ANCA-associated vasculitis** | Bowman's space/ glomerular capillaries/renal arterioles | • **Status**: partial.<br>• **Functional**: yes, kidney lesion evidence.<br>• **IDs**: none for kidney neutrophil proteomics.<br>• **Note**: blood neutrophil datasets are excluded. | • **Status**: none.<br>• **IDs**: none. | • **Status**: yes, human kidney.<br>• **IDs**: GEO GSE294965.[112]<br>• **Note**: Xenium plus one Xenium/ PhenoCycler slide; not neutrophil-centered. | Map MPO/PR3-exposed and NET-positive neutrophils directly at capillary lesions and crescents. | **High**. Proven drug target and a clear neutrophil role |
| **Anti-GBM disease** | Bowman's space/ glomerular capillaries | • **Status**: partial.<br>• **Functional**: yes, model/ intravital neutrophil evidence.<br>• **IDs**: none for kidney proteomics.<br>• **Note**: human kidney neutrophil proteomics not identified. | • **Status**: none.<br>• **IDs**: none. | • **Status**: yes, human/ model.<br>• **IDs**: GEO GSE294965.[112]<br>• **Note**: human Xenium plus model intravital/IF evidence. | Define the early pre-crescent neutrophil program before parietal epithelial activation dominates the lesion. | **Medium**. Rare, and the neutrophil role is secondary to antibody injury |
| **Atypical HUS** | Glomerular capillaries/renal arterioles/ peritubular capillaries | • **Status**: indirect.<br>• **Functional**: complement-endothelial TMA; neutrophil arm not established.<br>• **IDs**: none.<br>• **Note**: blood/plasma complement datasets are excluded. | • **Status**: none.<br>• **IDs**: none. | • **Status**: partial.<br>• **IDs**: none.<br>• **Note**: biopsy histology, TMA pathology and complement staining only | Define whether neutrophils are active downstream effectors of complement-mediated endothelial TMA in human kidney tissue. | **Medium**. Complement is already treatable, but the neutrophil role is unproven in human tissue |
| **C3 glomerulopathy** | Bowman's space/ glomerular capillaries | • **Status**: yes, human kidney.<br>• **IDs**: PXD045319.[113]<br>• **Note**: glomerular/deposit proteomics; not neutrophil-centered. | • **Status**: none.<br>• **IDs**: none. | • **Status**: yes, human kidney.<br>• **IDs**: Figshare doi:10.6084/m9.figshare.25249261.[114]<br>• **Note**: spatial transcriptomics exists; not neutrophil-centered. | Resolve whether neutrophils are lesion-level complement effectors or secondary inflammation markers, especially after complement inhibition. | **Medium**. A target exists, but it is unclear whether neutrophils drive injury or only mark it |

| | | | | | | |
|---|---|---|---|---|---|---|
| **IgA nephropathy** | Bowman's space/ glomerular capillaries/ interstitium | • **Status**: yes, human kidney.<br>• **IDs**: PXD032710.[115]<br>• **Note**: kidney tissue proteomics; not neutrophil-centered. | • **Status**: yes, human kidney.<br>• **IDs**: GEO GSE127136 (no linked publication); GSE171314; GSE286911.[116,117]<br>• **Note**: low neutrophil depth/undercaptured. | • **Status**: yes, human kidney.<br>• **IDs**: GEO GSE253439.[118]<br>• **Note**: CosMx spatial; not neutrophil-centered. | Focus neutrophil-state questions on active hematuric, proliferative, or crescentic flares rather than stable chronic IgAN. | **High**. Common, with a proven target, and the neutrophil role is clearest during flares |
| **Lupus nephritis** | Bowman's space/ glomerular capillaries/ interstitium | • **Status**: partial.<br>• **Functional**: yes, LDG/ NET literature.<br>• **IDs**: none for kidney neutrophil proteomics.<br>• **Note**: blood proteomics excluded from dataset IDs. | • **Status**: yes, human kidney.<br>• **IDs**: dbGAP phs001457.v1.p1.[119]<br>• **Note**: low neutrophil depth/undercaptured. | • **Status**: yes, human kidney.<br>• **IDs**: GEO GSE294965.[112]<br>• **Note**: Xenium spatial includes lupus nephritis; not dissociation scRNA. | Link circulating LDGs and NET markers to spatially defined intrarenal neutrophils in active class III/IV lesions. | **High**. Common and treatable, with strong neutrophil and NET evidence |
| **Post-infectious /infection-related GN** | Bowman's space/ glomerular capillaries | • **Status**: none.<br>• **Functional**: neutrophil-rich histology.<br>• **IDs**: none.<br>• **Note**: complement/pathology evidence; no neutrophil proteomics found. | • **Status**: none.<br>• **IDs**: none. | • **Status**: partial.<br>• **IDs**: none.<br>• **Note**: IF/histology only; no spatial-omics accession found. | Profile acute resolving lesions separately from persistent infection-related GN and C3G-like complement persistence. | **Low**. Usually resolves on its own, so there is little to target |
| **STEC-HUS** | Glomerular capillaries/ peritubular capillaries | • **Status**: partial.<br>• **Functional**: yes, Shiga toxin/endothelial TMA with NET evidence.<br>• **IDs**: none.<br>• **Note**: no kidney neutrophil proteomics found. | • **Status**: none.<br>• **IDs**: none. | • **Status**: partial.<br>• **IDs**: none.<br>• **Note**: TMA histology and IF/IHC only; no spatial-omics accession found. | Determine whether NETs are causal, amplifying, or mainly biomarkers of toxin-endothelial and platelet injury. | **Medium**. Care is supportive, and it is unclear whether NETs cause injury or only mark it |

(*Continued*)

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**Table 1** (Continued).

| Disease Context | Renal Compartments | Proteomics/Functional Evidence | scRNA-seq/snRNA-seq Neutrophil Capture | Spatial or Imaging Evidence | Main Unresolved Gap/Next Experiment | Research Priority |
|---|---|---|---|---|---|---|
| **Advanced CKD / SIDKD** | Interstitium/ peritubular capillaries | • **Status**: none.<br>• **Functional**: systemic uremic neutrophil dysfunction described.<br>• **IDs**: none. | • **Status**: none.<br>• **IDs**: none. | • **Status**: partial.<br>• **IDs**: none.<br>• **Note**: CKD/fibrosis spatial data exist, but not neutrophil-state centered. | Connect uremic toxins, dialysis modality, infection risk, NET propensity, and cardiovascular inflammation in one longitudinal framework. | **High**. Very common, but how uremia alters neutrophils is poorly mapped |
| **AKI-to-CKD transition** | Interstitium/ outer medulla/ peritubular capillaries | • **Status**: yes, mouse kidney.<br>• **IDs**: PXD010861; PXD065974.[120,121]<br>• **Note**: kidney tissue proteomics; not neutrophil-centered. | • **Status**: yes, mouse and human kidney.<br>• **IDs**: GEO GSE161201; GSE267242; GSE210622.[122–124]<br>• **Note**: low neutrophil depth/undercaptured. | • **Status**: partial, mouse.<br>• **IDs**: GEO GSE267242.[123]<br>• **Note**: spatial included in AKI-to-CKD model; not neutrophil-centered. | Capture neutrophils across injury, failed resolution, efferocytosis failure, and fibrosis onset in the same time course. | **High**. Common with no targeted therapy, and failed resolution is central but understudied |
| **Chronic allograft injury/ chronic interstitial nephritis** | Interstitium/ peritubular capillaries | • **Status**: yes, human allograft kidney.<br>• **IDs**: PXD064523.[125]<br>• **Note**: biopsy proteomics; not neutrophil-specific. Non-transplant chronic interstitial nephritis remains less defined. | • **Status**: yes, transplant kidney.<br>• **IDs**: GEO GSE166775; EGA EGAD00001015631.[126,127]<br>• **Note**: not neutrophil-centered; disease meaning is context-dependent. | • **Status**: partial.<br>• **IDs**: none.<br>• **Note**: transplant spatial approaches emerging; no neutrophil-centered accession found. | Separate neutrophils in rejection, infection, drug injury, and chronic scarring before treating them as one interstitial signal. | **Medium**. Several different causes that must be told apart before treating |
| **Cholesterol crystal embolism** | Peritubular capillaries/renal arterioles | • **Status**: partial.<br>• **Functional**: yes, crystal clot, C5a/C5aR, GSDMD and platelet evidence.<br>• **IDs**: none. | • **Status**: yes, mouse kidney.<br>• **IDs**: GEO GSE298484.[128] | • **Status**: yes, model pathology.<br>• **IDs**: none.<br>• **Note**: IF/histology and vascular lesion imaging. | Validate whether human CCE lesions contain equivalent neutrophil, complement, platelet, and GSDMD-linked states. | **High**. Strong neutrophil mechanism in models, not yet confirmed in human tissue |

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|---|---|---|---|---|---|---|
| **Ischemia-reperfusion injury** | Outer medulla/ peritubular capillaries | • **Status**: yes, mouse kidney.<br>• **IDs**: PXD020708 (no linked publication); PXD065974;[121] PXD038339.[129]<br>• **Note**: kidney proteomics; not neutrophil-centered. | • **Status**: yes, mouse kidney.<br>• **IDs**: GEO GSE161201; GSE267242.[122,123]<br>• **Note**: low neutrophil depth/undercaptured. | • **Status**: yes, model imaging.<br>• **IDs**: GEO GSE267242.[123]<br>• **Note**: intravital/IF/ NET histology; no canonical human spatial accession found. | Pair neutrophil state capture with no-reflow imaging, endothelial injury, and tubular necrosis in the same animals/time points. | **High**. Very common and relevant to transplantation, with NETs strongly implicated |
| **Sepsis-associated AKI** | Outer medulla/ peritubular capillaries | • **Status**: yes, mouse kidney.<br>• **Functional**: yes, NET/ PAD4/septic AKI literature.<br>• **IDs**: PXD017045.[130]<br>• **Note**: kidney proteome/ phosphoproteome; not neutrophil-centered. | • **Status**: yes, mouse kidney.<br>• **IDs**: GEO GSE151658.[131]<br>• **Note**: low neutrophil depth/undercaptured. | • **Status**: partial.<br>• **IDs**: none.<br>• **Note**: IF/histology and endothelial/NET markers; no kidney spatial-omics accession found. | Separate systemic septic neutrophil programs from kidney-local capillary congestion, endothelial injury, and tubular stress. | **High**. Common and often fatal. NETs both injure and defend, a balance still to resolve |
| **Acute pyelonephritis/ ascending UTI** | Interstitium/ tubule lumen | • **Status**: partial.<br>• **Functional**: yes, mouse UTI kidney models and IF/ histology.<br>• **IDs**: none.<br>• **Note**: urine or systemic proteomics excluded from dataset IDs. | • **Status**: yes, mouse kidney.<br>• **IDs**: GEO GSE296327.[132]<br>• **Note**: low neutrophil depth/undercaptured. | • **Status**: yes, human kidney.<br>• **IDs**: GEO GSE253439.[118]<br>• **Note**: CosMx in advanced pyelonephritis; not acute pyelonephritis and not neutrophil-centered. | Add granulocyte-preserving or fixed-RNA scRNA-seq to infected kidney, paired with epithelial injury and bacterial clearance readouts. | **Medium**. Neutrophils are protective here, and the main hurdle is capturing them in sequencing |

**Notes**: Status indicates whether kidney-based evidence exists for neutrophil-state characterization within each modality. "Yes" means kidney data are available, but not necessarily neutrophil-specific. "Partial" means functional, imaging, pathology, or non-neutrophil-specific evidence exists, but neutrophil-state resolution is limited. "Indirect" means evidence supports the disease mechanism but does not define an intrarenal neutrophil state. "None" means no relevant kidney neutrophil-focused dataset was identified. Dataset IDs are listed only for kidney-related datasets; blood, urine, and systemic datasets are not included. Neutrophils are often underrepresented in scRNA-seq/snRNA-seq because of low RNA content, granule-associated nuclease activity, and loss during tissue dissociation. Research priority (High, Medium, or Low) reflects the strength of evidence implicating neutrophils as drivers, the availability of a tractable neutrophil target, and the size of the evidence gap and disease burden. It is a qualitative author judgment, not a formal score.

**Abbreviations**: AKI, acute kidney injury; ANCA, anti-neutrophil cytoplasmic antibody; anti-GBM, anti-glomerular basement membrane; C3, complement component 3; C5a, complement component 5a; C5aR, C5a receptor; CCE, cholesterol crystal embolism; CKD, chronic kidney disease; CosMx, CosMx spatial molecular imaging platform; EGA, European Genome-phenome Archive; GEO, Gene Expression Omnibus; GN, glomerulonephritis; GSDMD, gasdermin D; HUS, hemolytic uremic syndrome; ID, identifier; IF, immunofluorescence; IgA, immunoglobulin A; IgAN, IgA nephropathy; IHC, immunohistochemistry; LDG, low-density granulocyte; MPO, myeloperoxidase; NET, neutrophil extracellular trap; PAD4, peptidylarginine deiminase 4; PhenoCycler, PhenoCycler multiplexed spatial imaging platform; PR3, proteinase 3; PXD, ProteomeXchange dataset identifier; scRNA-seq, single-cell RNA sequencing; SIDKD, secondary immunodeficiency related to kidney disease; snRNA-seq, single-nucleus RNA sequencing; STEC-HUS, Shiga toxin-producing *Escherichia coli* hemolytic uremic syndrome; TMA, thrombotic microangiopathy; UTI, urinary tract infection; Xenium, Xenium in situ spatial imaging platform.

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## Generative AI Disclosure

OpenAI imaging tools accessed through ChatGPT 5.5 were used to generate the illustration shown in Figure 1, which was manually edited and labeled by the authors. AI was also used to assess formatting requirements according to publication guidelines. The authors confirm the originality and accuracy of the content of Figure 1. They have reviewed the terms of use of the tool and consider its output suitable for publication. They have the right to publish the generated image and have obtained any permissions required. They take full responsibility for the integrity of the whole content, including the accuracy of all references.

## Abbreviations

AAV, ANCA-associated vasculitis; AKI, acute kidney injury; ANCA, anti-neutrophil cytoplasmic antibody; anti-GBM, anti-glomerular basement membrane; C3, complement component 3; C5a, complement component 5a; C5aR1, complement component 5a receptor 1; CCE, cholesterol crystal embolism; CKD, chronic kidney disease; DAMP, damage-associated molecular pattern; GSDMD, gasdermin D; HIF-1α, hypoxia-inducible factor 1α; IgA, immunoglobulin A; IRI, ischemia-reperfusion injury; LDG, low-density granulocyte; MPO, myeloperoxidase; NET, neutrophil extracellular trap; PAD4, peptidylarginine deiminase 4; PR3, proteinase 3; ROS, reactive oxygen species; SIDKD, secondary immunodeficiency related to kidney disease; STEC-HUS, Shiga toxin-producing Escherichia coli-associated hemolytic uremic syndrome; TMA, thrombotic microangiopathy; UTI, urinary tract infection.

## Data Sharing Statement

No new datasets were generated or analyzed for this review. Publicly available datasets discussed in the article are cited in the references.

## Author Contributions

John Ku: conceptualization, data curation, investigation, visualization, writing – original draft, and writing – review and editing.

Kailey K Flora: investigation and writing – review and editing.

Stefanie Steiger: investigation, supervision, and writing – review and editing.

Hans-Joachim Anders: conceptualization, supervision, and writing – review and editing.

All authors gave final approval of the version to be published, have agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

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