Brief Histopathologic Overview about Acute Kidney Injury

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Abstract

Background: Acute kidney injury (AKI) is a clinical syndrome that complicates the course and worsens the outcome in a significant number of hospitalised patients. Recent advances in clinical and basic research will help with a more accurate definition of this syndrome and in the elucidation of its pathogenesis. With this knowledge we will be able to conduct more accurate epidemiologic studies in an effort to gain a better understanding of the impact of this syndrome. AKI is a syndrome that rarely has a sole and distinct pathophysiology. Recent evidence, in both basic science and clinical research, is beginning to change our view for AKI from a single organ failure syndrome to a syndrome where the kidney plays an active role in the progress of multi-organ dysfunction. Accurate and prompt recognition of AKI and better understanding of the pathophysiologic mechanisms underlying the various clinical phenotypes are of great importance to research for effective therapeutic interventions

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Acute kidney injury (AKI), previously called acute renal failure (ARF), is a condition of sudden kidney failure in patients with or without preexisting chronic kidney disease (CKD); severe kidney dysfunction within a few hours or days results in a significant decrease (oliguria) or complete elimination of urine (anuria), with electrolyte imbalance, often requiring hemodialysis.

While it is unclear when AKI was first recognized, incidences are scattered in the medical literature over the centuries (http://www.renalmed.co.uk). Most experts agree that the pathology was first described during World War II when four cases of crush injury characterized by diffuse acute tubular damage with pigmented casts followed by impaired renal function were reported [1]. Homer W. Smith introduced the term 'ARF' in 1951 [2]. In 2004, ARF was replaced by AKI [3, 4]. Before 2004 there were at least 35 ARF definitions. This situation of having various definitions has given

rise to a wide range of incidence estimates for AKI from 1 to 25% of intensive care unit (ICU) patients and has led to mortality rate estimates from 15 to 60% [5, 6].

AKI is now defined by the RIFLE criteria (risk, injury, failure, loss, end-stage kidney disease) and is not just ARF. It incorporates the entire spectrum of the syndrome, from minor changes in renal function to the requirement for renal replacement therapy [7]. In practice, most nephrologists follow the Kidney Disease: Improving Global Outcomes (KDIGO) criteria, which recommend determining the cause of AKI whenever possible [5, 6]. The incidence of AKI on renal biopsy is not entirely known, but is common either as an isolated finding or concurrent with other diseases. This review is an account of the spectrum of entities identified on renal biopsy from patients presenting with AKI.

AKI clinical and pathologic classifications

It should be remembered that AKI is a clinical term. Pathologists use descriptive pathologic findings that cumulate to the term 'acute tubular injury' (ATI). Prerenal, intrarenal, postrenal and even unilateral insults can cause ATI. A dissociation between structural and functional changes was first recognized at autopsy of World War II soldiers with acute kidney failure and death who were found to have mild kidney findings (so-called shock kidneys) [1]. Examples of dissociation between clinical symptoms and histopathological findings include prerenal AKI caused by volume depletion as in cardiogenic, allergic or hemorrhagic shock. In such cases, ATI may be mild and/or even absent. Postrenal AKI is caused by urinary flow obstruction and can be unilateral or bilateral, e.g. unilateral hydronephrosis, lithiasis and/or pyelonephritis. The recent AKI classification that includes categories designated as declining renal function (glomerular filtration rate) instead of renal failure are in range and extent the histopathological ATI spectrum [6]. In practice, a semiquantitative histopathological scoring of ATI as mild, moderate or severe (or focal versus diffuse) is preferable instead of the term acute tubular necrosis (ATN), which was previously used despite the absence of necrosis in many cases.

Histopathological definitions of AKI

ATI is characterized by focal or diffuse tubular luminal dilatation, simplification of the lining epithelium, loss of the brush border in proximal tubules, loss of nuclei and/or the presence of nucleoli (Figure 1A). Epithelial cell mitoses and cytoplasmic basophilia can also be seen and are thought to represent epithelial cell regeneration. Both proximal and distal tubules can be affected by ATI. ATN is characterized by focal or diffuse tubular epithelial cell coagulative-type necrosis and detachment from the basement membrane (Figure 1B and C). Epithelial cell necrosis consists of cytoplasmic swelling (oncosis), degeneration of cytoplasmic organelles and a ghost-like tubular appearance staining dark pink on hematoxylin and eosin (H&E) stain. ATN is much less common compared with ATI and requires prolonged and sustained tubular injury that is usually absent in acute AKI. The exception is cortical necrosis caused by an acute ischemic process, leading to

degeneration of large number of tubules (coagulation necrosis). ATI and ATN may coexist (Figure 1C).

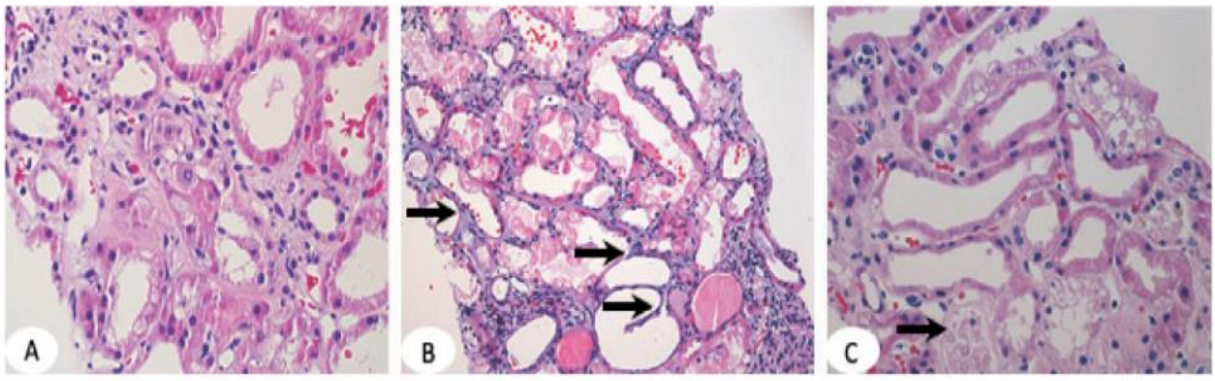


FIGURE 1: (A) ATI in proximal tubules shows luminal dilatation, simplification of the lining epithelium and loss of epithelial cell nuclei in some cells and loss of the brush border. (B) ATN is defined by tubular epithelial cell necrosis (dark pink fragmented cytoplasm with no nuclei) and denudation of the basement membrane (arrows). (C) ATI and ATN in the same renal biopsy. Arrow points to necrotic tubules. Dilated tubules are lined by a thin epithelial layer with no brush border. H&E,×100.

Intrarenal AKI is associated with numerous diseases, including glomerular, tubulointerstitial and vascular. Intrinsic toxic insults to tubular epithelial cells include heavy proteinuria, hematuria, interstitial nephritis and ischemia secondary to microvascular (endothelial) injury, e.g. renal vasculitis and thrombotic microangiopathies (TMAs). Glomerular diseases, acute or chronic, can be complicated by ATI. Examples include diabetic nephropathy, immunoglobulin A (IgA) nephropathy, hypertensive kidney disease, myeloma cast nephropathy, transplant rejection and TMAs.

ATI with distinct pathology

Rhabdomyolysis

Rhabdomyolysis causes ARF in 7–15% of all AKI cases in the USA and affects 13–50% of hospitalized patients, with worse prognosis and greater mortality in critically ill patients [8]. In our recent study of renal biopsies accrued from 2011 through June 2014 among 27 850 renal biopsies in our search, 249 biopsies (~1%) were positive for myoglobin casts [9]. On H&E stain, myoglobin casts are focal, light pink, almost translucent, but may vary from pink to dark red, granular or chain-like clumps (Figure 2A). Myoglobin casts are difficult to diagnose accurately because they have overlapping morphology with hemoglobin casts, myeloma casts and Tamm–Horsfall protein casts. Myoglobin immunohistochemistry is very helpful in arriving at a definitive diagnosis, highlighting greater numbers of injured tubules (not obvious on H&E) by staining luminal deposits (casts) and/or proximal and occasionally collecting duct epithelium (Figure 2B). Notably, ATI marked by the kidney injury molecule-1 (KIM-1) antibody is more widespread, highlighting the majority of tubules, compared with focal myoglobin staining (Figure 2C). KIM-1 is not currently routinely used

to assess ATI in renal biopsies even though it is US Food and Drug Administration approved as a biomarker believed to participate in the process of both AKI and healing [10].

The pathogenesis of rhabdomyolysis is attributed to the release of myoglobin into the circulation, subsequently filtered by the glomeruli and cleared in the tubules where it accumulates either as tubular myoglobin casts or intraepithelial deposits with either a ropey or finely granular appearance [9]. Diagnosing rhabdomyolysis clinically is complicated by frequently absent classic clinical symptoms (triad of muscle pain, weakness and dark urine) and/or nondiagnostic values of laboratory tests such as creatine phosphokinase (CPK). CPK increases within 12 h of the onset of muscle injury, has a serum half-life of ~36 h and declines 3–5 days after cessation of muscle injury [11]. At the time of biopsy, CPK may already have dissipated. The exact mechanism of ATI due to myoglobin pigment deposits is still debated but it is thought that myoglobin itself rarely leads to kidney injury in the absence of other risk factors such as ischemia, volume depletion and hypotension. Acid urine enhances the renal toxicity of myoglobin by converting heme in myoglobin to ferrihemate (hematin), shown to produce free hydroxy radicals that are directly toxic to renal tubular epithelial cells or via renal vasoconstriction due to inhibition of nitric oxide synthesis. In addition, the heme fraction of myoglobin induces the release of free radicals, further contributing to ischemic tubular damage [9].

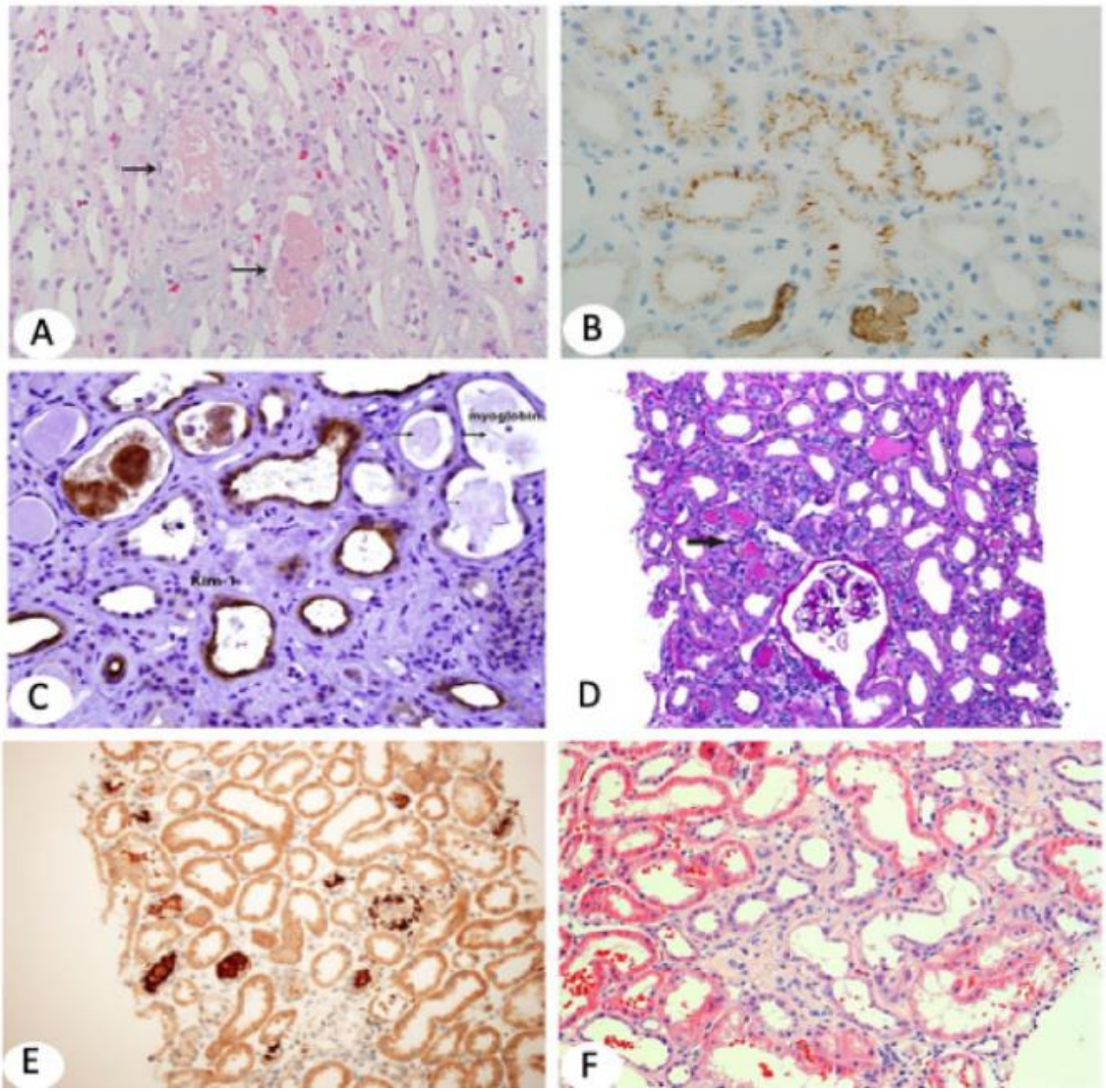
Underlying etiologies of myoglobin casts include drugs of abuse (heroin, cocaine, opioids), infections [including human immunodeficiency virus (HIV)], bacterial sepsis, chemotherapy and immunosuppression (transplantation medicines, e.g. rapamycin), dehydration (intense exercise), malignant hypertension, trauma (surgery, traffic accidents) and myopathies [12] . The importance of making the correct diagnosis of rhabdomyolysis has prognostic implications. Full renal function recovery occurs in about half of the patients; the rest remain dialysis dependent or progress to CKD [9].

Hemoglobinuria and red blood cell casts, including Coumadin nephropathy and hemosiderosis

Heme proteins can cause AKI via at least three mechanisms: direct cytotoxicity of released hemoglobin products, decreased renal perfusion and interaction of the intratubular hemoglobin with Tamm–Horsfall protein (hemoglobin casts). Free hemoglobin is bound to serum haptoglobin; when haptoglobin is saturated, free plasma hemoglobin dissociates to dimeric molecules that filter more easily through the glomeruli. Hemoglobin is taken up by the megalin–cubilin receptors on the apical surface of tubular epithelium and deposits into proximal tubules [9]. Intracellular hemoglobin dissociates into heme and globin and heme is degraded by heme oxygenase (HO). The inducible HO-1 isoform increases rapidly, accompanied by increased intracellular ferritin. These intracellular reactions lead to binding of iron to ferritin. Even though the response is aimed to diminish damage to cytoplasmic organelles, mitochondrial injury occurs by impairment of mitochondrial oxygenation. Tubular epithelial cell apoptosis, oxidative stress and release of pro-inflammatory cytokines follow.

Other organs, such as the liver and lungs, are more likely to be affected because the hemoglobin–haptoglobin complex is too large to be filtered by the glomerulus. Therefore hemoglobin deposits rarely cause AKI.

On light microscopy, hemoglobin casts appear pale or granular and closely resemble myoglobin casts. Occasionally hemoglobin appears light brown. Immunohistochemistry with antibodies to hemoglobin is the only way to reliably distinguish from myoglobin casts (Figure 2D and E). Of note, renal biopsies with myoglobin-positive casts may also have evidence of hemolysis in the background. Intact red blood cells (RBCs) also stain with hemoglobin stain (internal control). Strenuous exercise, hemolysis secondary to infection (case shown in Figure 2D and E), incompatible blood transfusion and hematologic disorders are common causes of hemoglobinuria [13, 14]. Another reported cause of hemoglobinuria is transurethral prostate resection when distilled water is used as an irrigant [15].



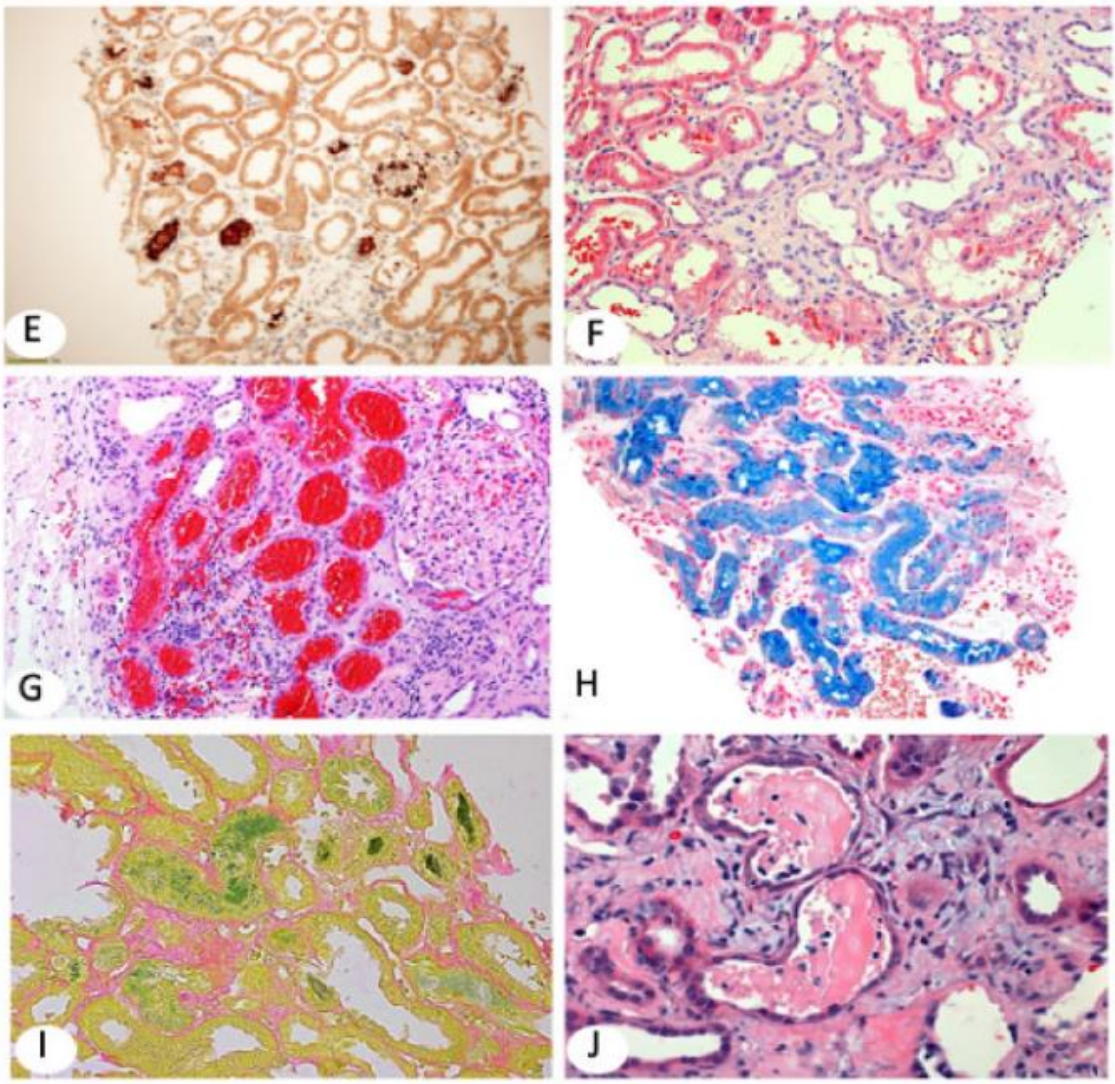


FIGURE 2: (A) Myoglobin casts involve focal tubules and appear light pink on H&E (100). Arrows point to myoglobin casts. (B) Myoglobin stains tubular casts brown and may also stain tubular epithelial brush border and/or cytoplasm in a punctuate pattern. Immunohistochemistry (IHC) 100. (C) KIM-1, a marker for AKI, is overexpressed in injured and simplified (thin) tubular epithelium [same biopsy as in (B)]. KIM-1 IHC 200. (D, E) The biopsy shows ATI with focal translucent tubular casts (arrow in D). Hemoglobin IHC highlights the tubular casts (E). Myoglobin stain was negative. The patient in (D–E), a 72-year-old Caucasian man with severe coronary artery disease, hypertension (HTN) and type 2 diabetes developed recurrent infection on his right foot, treated with intravenous piperacillin/tazobactam and developed chills and shortness of breath. He also had hematuria and severe peripheral hemolysis. CPK was normal; creatinine increased to 7 mg/dL with low C3 and C4. Clinical diagnoses included all comorbidities, but hemoglobin nephropathy was

least expected. Hemoglobin IHC 100. (F) Patient with IgA nephropathy who presented with hematuria and AKI. Renal biopsy shows tubular dilatation, simplification of the epithelium and multifocal luminal RBCs (H&E 100). (G) Large patch of subcapsular proximal tubules packed with RBCs. Renal biopsy is from a 79-year-old white woman who presented with AKI on CKD. She has a histroy of atrial fibrillation on Coumadin. (I) Faucet stain marking bilirubin casts (100). The patient was a 50-year-old Caucasian man with kidney transplant and AKI. Serum creatinine was 3.9 mg/ dL and bilirubin and liver function tests were increased. (H) Marked tubular iron deposits with Prussian blue stain. The patient is a 60-year-old African American man who presented with AKI, macroscopic hematuria, hemolysis 1þ and increased reticulocytes. He had a history of mitral valve replacement, congestive heart failure and anemia. The differential diagnosis included cardiac valve defect, sickle cell disease and/or supratherapeutic international normalized ratio (H&E 100). (J–L) Diffuse ATI and typical multiple myeloma casts that appear as partially crumbled luminal protein deposits admixed with inflammatory cells.

Gross or microscopic hematuria manifested by large amounts of RBCs in the urine may cause ATI by tubular obstruction. Hematuric syndromes, e.g. IgA nephropathy (Figure 2F), or minimal change disease presenting with hematuria, vasculitis and anticoagulation are the most frequent causes of obstructive ATI caused by RBC casts.

Anticoagulation nephropathy has potentially fatal consequences, particularly in patients with CKD. Clinical presentation with AKI is sometimes without overt creatinine changes, thus so-called warfarin nephropathy can be clinically overlooked. The incidence and severity were only recently recognized [16, 25]. Renal biopsy typically shows large numbers of intratubular RBC casts associated with tubular epithelial thinning, luminal dilation and loss of brush border (Figure 2G).

Hemosiderosis is a known complication of chronic hemolytic anemias, including paroxysmal nocturnal hemoglobinuria, and mechanical cardiac valves with residual valvular regurgitation or perivalvular leak. ATI is due to hemosiderin, an iron storage complex. The breakdown of heme gives rise to biliverdin and iron. Released iron is trapped and stored as hemosiderin in tissues. Hemosiderin is also generated from the abnormal metabolic pathway of ferritin. With H&E, hemosiderin stains as brown and granular deposits within tubular epithelial cells. Prussian blue iron specifically stains hemosiderin deposits (Figure 2H). Additional causes of hemosiderosis include sepsis, iron overload as in hereditary hemochromatosis and multiple transfusions for sickle cell disease. Some cases of infectious hemosiderosis may be reversible. For example, while *Clostridium difficile*–induced hemolysis may be complicated by hemoglobinuria-induced ATI, rarely is hemosiderosis reported; these deposits may resolve with resolution of the infection [18-35]. Supratherapeutic doses of Coumadin and other blood thinners (e.g., dabigatran) should also be excluded in patients with artificial valves or heart disease since anticoagulation is routinely prescribed.

AKI pathophysiology

An increased understanding of the pathophysiology underlying AKI was revealed in the last few decades through molecular and animal studies that show oxidative stress [47], endothelial injury [36-48], mitochondrial injury (best described in the HIV) population treated with antiretroviral medications] [49] and innate immunity as central mechanisms [50], discussed briefly below.

AKI, previously thought to be a relatively benign process without significant long-term sequelae, is now considered a long-term risk factor for CKD, particularly in older patients with coexisting comorbidities, particularly sepsis, affecting 40–70% of patients in the ICU [51, 52].

Therapeutic or illicit drugs and toxins represent external insults. Numerous drugs can cause ATI/ATN. The most common are antibiotics (e.g. vancomycin), chemotherapeutics, angiotensin-converting enzyme inhibitors, lithium and over-the-counter supplements. Similar patterns of tubular injury have been reported in association with illicit drugs such as opioids and synthetic cannabinoids (Spice, K2, etc.) [49, 53–55]. Drugs are such a common cause of ATI/ATN that, above and beyond any other causes, drug exposure should first and foremost be clinically excluded.

Interesting mechanisms of infection-induced ischemic AKI continue to be found. For example, neutrophil extracellular traps damage the kidney through neutrophil arginine deiminase 4 [56, 57].

Animal models of AKI

A significant amount of research has been directed at investigating AKI pathophysiology and developing AKI therapeutics in animal models [58, 59]. However, none of these therapies have translated into clinical care to date. One of the most widely used animal models of AKI is the ischemia–reperfusion model. A warm ischemia–reperfusion study is typically performed by unilateral or bilateral clamping of the renal vasculature for 30–45 min followed by reperfusion for 1–2 days [59, 60]. This model was extensively studied in pigs, dogs, rabbits, rats and mice. Toxin exposure is a known cause of AKI and has been used to study AKI pathophysiology *in vivo*. Cisplatin, folic acid, aristolochic acid and warfarin are common nephrotoxins utilized to induce AKI in animal models [51–65]. Rhabdomyolysis is a specific clinical condition that may be reproduced in animals using a glycerol model of AKI. Glycerol injected into the hind leg muscles of rats produces rapid AKI and rhabdomyolysis [66, 67]. The unilateral ureteral obstruction model is a reproducible animal model whereby a single ureter is ligated, resulting in mechanical stress and inflammation in one kidney. This model is used to study the AKI to CKD transition. Sepsis is another well-documented cause of AKI [51, 68]. Studying this process in animals may be performed by lipopolysaccharide injection or by using the more clinically relevant cecal ligation and puncture (CLP) model [69, 70]. Although the CLP model is more typical of the human condition, it is less reproducible and more technically

challenging. Animal models are a useful tool to investigate the pathophysiology of AKI. However, the dearth of new clinically useful therapeutics developed using these animal models highlights the disconnect between human clinical AKI and preclinical studies. This underscores the point that clinical AKI in humans is a diverse process with multiple etiologies and varying pathophysiology such that single treatment options are unlikely to prove effective.

AKI biomarkers

Current clinical practice utilizes serum creatinine and urine output to identify patients with AKI, regardless of the underlying etiology. A significant achievement has been standardizing AKI diagnostic criteria by the KDIGO [5, 71, 72]. Serum creatinine may not increase until days following injury, may change in cases without structural kidney damage and may not change despite injury in patients with significant renal reserve [73–75]. Due to these known imperfections, a troponin-like biomarker for AKI is desired. The hope is to facilitate early diagnosis in order to implement current management strategies aimed at preventing further injury. Earlier diagnosis may facilitate reexamination of therapeutics that previously failed clinical trials, possibly due to delayed treatment using creatinine for therapeutic initiation.

The last decade has seen a significant effort to identify sensitive and specific urine and plasma AKI biomarkers. AKI biomarkers may be functional (cystatin C), related to damage (myo-inositol oxygenase, N-acetyl-β-glucosaminidase, glutathione S-transferase, alkaline phosphatase), inflammatory (interleukins-18, -6, -10 and -5), upregulated in the proximal tubule following injury (KIM-1), upregulated in the distal tubule following injury (neutrophil gelatinase–associated lipocalin) or cell cycle arrest indicators (tissue inhibitor metalloproteinase-2 and insulin-like growth factor binding protein-7) [76, 77]. Despite extensive research and development of standardized assays for some biomarkers, AKI biomarkers have predominantly been restricted to research use and have not yet permeated clinical practice. One reason for this discrepancy is the use of creatinine as a flawed gold standard for biomarker qualification [76]. Another drawback is their lack of specificity for renal disease [7]. One biomarker, myo-inositol oxygenase, is reportedly restricted to renal tissue and shows promise as a renal-specific proximal tubular damage indicator but has yet to undergo significant investigation [76]. Utilizing other criteria such as need for dialysis and mortality has helped to identify biomarkers that complement clinical assessment [78–80]. Despite these shortcomings, recent studies indicate a possible role for biomarkers in discriminating true AKI from prerenal azotemia, hepatorenal syndrome and cardiorenal syndrome [78]. Future studies will need to assess the ability of AKI biomarkers to improve patient outcomes in order to be widely adopted in clinical practice [77].

CONCLUSIONS

The pathology of AKI is as diverse as the entities causing it. Renal biopsy illuminates this diversity and provides specific diagnoses using available immunohistochemical or histochemical stains to

complement routine pathologic evaluation. Interpretation and effective consultation require highly skilled and sophisticated renal pathologists and clear communication with the treating nephrologists. Renal biopsy pathology is frequently the fastest and most accurate procedure in determining the specific cause of AKI, as shown below. Furthermore, in spite of the existing clinical AKI criteria and worldwide validation, there is still inconsistency in the application of criteria confounded by the limitations of serum creatinine and urine output as AKI biomarkers.

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