Expanding the Role for Kidney Biopsies in Acute Kidney Injury

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Summary: Acute kidney injury (AKI) is a highly heterogeneous, common, and potentially devastating condition associated with markedly increased hospital length of stay, cost, mortality, and morbidity. Expanding the role for kidney biopsies in AKI may offer fresh insights into disease heterogeneity, molecular mechanisms, and therapeutic targets. A number of challenges face investigators and clinicians considering research biopsies in AKI: ensuring patient safety, ensuring the ethical conduct of research studies, and maximizing the scientific yield of the kidney tissue obtained. The societal benefits of research that lead to novel strategies for preventing and treating AKI would be enormous. Rethinking our current approach to the role of kidney biopsy for AKI diagnosis and research may be a major step toward the promise of personalized medicine in nephrology.

Keywords: Acute kidney injury, biopsy, histopathology, pathogenesis

In 1950, Homer Smith[1] made an astute observation on acute kidney injury (AKI) that we would be well served to remember today: "No constant pathological picture has been observed, nor is it expected in a variety of circumstances where uncomplicated renal ischemia, renal edema, pigment casts, and nephrotoxins (carbon tetrachloride) contribute varying elements to the renal debacle. It would seem better to describe the lesions in such kidneys as they are observed, rather than attempt to categorize them under a convenient and frequently misleading label." In the nearly 70 years since the publication of Smith's[1] textbook *The Kidney*, much attention has been focused on consensus criteria for AKI, which Smith aptly described as "a convenient and frequently misleading label." Far less attention has been paid, especially recently, to "describing the lesions as they are observed"[1] through histopathologic evaluation of kidney tissue. In this review we aim to make a case for expanding the role of biopsies for diagnosis and research in AKI to better characterize the lesions and many subendophenotypes that we often classify as a single entity.

AKI refers to an extremely heterogeneous group of clinical conditions that share common diagnostic features: an increase in the serum creatinine concentration and/or a decrease in urine output. These two elements that comprise the diagnostic criteria for AKI reflect major life-sustaining functions of the kidneys, which are to clear the blood of waste products and to regulate circulating plasma volume. A wide array of conditions can acutely injure or impair kidney function and result in a diagnosis of AKI, including tubular injury, tubulointerstitial nephritis, glomerulonephritis, and prerenal azotemia. Despite the anatomic references to tubules, the interstitium, and the glomeruli inherent in many clinicopathologic diagnoses of AKI, kidney biopsies for pathologic confirmation and diagnosis are performed very rarely.

THE HISTORY OF DIAGNOSIS AND DESCRIPTIONS OF AKI

As reviewed by Eknoyan[2] in "Emergence of the Concept of Acute Kidney Injury," the entities we classify as AKI have gone by a multitude of different names. "Ischuria renalis," first described by Morgagni[2] and then by Abercrombie,[3] indicated suppression or retention of urine (anuric AKI), which historically was the only diagnostic clue to AKI. Later, with the introduction of microscopic evaluation of pathologic material and with the introduction of chemical analyses of bodily fluids, diagnosis of AKI expanded to include laboratory criteria and pathologic findings.[4] In Osler's[5] "Principles and Practice of Medicine" the chapter on Acute Bright's Disease refers to what we would today call AKI secondary to nephrotoxins, pregnancy complications, burns, and trauma. In "The Kidney," Smith[11] introduced the term *acute renal failure* and described the available animal and human studies in the literature. The clinical causes of acute renal failure described in Smith's textbook included shock (hemorrhagic, septic, burns, post-partum), toxins (sulfathiazole, carbon tetrachloride, uranium), crush syndrome, and intravascular hemolysis.

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It is remarkable how different AKI (in the developed world) is today compared with reports in the 18th through the early 20th centuries (Table 1). Our conceptualization of the clinical course of AKI derives from those earlier reports, before the advent and widespread use of procedures and nephrotoxic drugs so characteristic of AKI today: cardiopulmonary bypass, intravenous contrast agents, nephrotoxic antibiotics, anticancer treatments, and vasopressors for hemodynamic support during multiorgan failure, to name just a few. The widely taught sequence of events occurring in AKI—the initiation, maintenance, extension, and recovery phases[6]—is based on reports of the natural history of severe oligoanuric AKI, starting with Bywaters and Beall[7] in 1941 (AKI from crush injuries), Muirhead et al[8] in 1948 (AKI from incompatible blood transfusions and other causes), Bull et al[9] in 1950 (AKI from multiple causes),[9] and Swann and Merrill[10] in 1953 (AKI from multiple causes). The 75-page article, "The Clinical Course of Acute Renal Failure," by Swann and Merrill[10] described the clinical details of 85 patients, who had an average age of 45 years and an average peak blood urea or nonprotein nitrogen concentration of 185 mg/dL. The causes of AKI in the report by Swann and Merrill[10] included a number of unfamiliar or uncommon diagnoses in today's hospitals, such as transfusion reactions (25%), distilled water irrigation or infusion (9%), and carbon tetrachloride toxicity (8%), in addition to more recognizable entities such as postoperative hemorrhage (21%). Reports in the 1960s and 1970s updated the conceptualization of AKI to include the increasingly more common nonoliguric forms. Vertel and Knochel[11] from the US Army Surgical Research Unit, for example, described in an article titled "Nonoliguric Acute Renal Failure," 11 cases of nonoliguric AKI, 10 of which were from burns, and 14 cases of postburn oliguric AKI. AKI now is diagnosed in the context of more timely diagnosis from frequent measurements of blood chemistries, improvements in volume resuscitation and hemodynamic monitoring, and the introduction of nephrotoxic drugs and procedures, all of which have led to the changing phenotype of AKI, which now is estimated to complicate 6% to 20% of hospital admissions, depending on the definition used.[12–14]

Most reports of the histopathology of AKI in humans are from the earlier era when AKI was diagnosed at its most severe form. In 1951, Oliver et al[15] published detailed morphologic descriptions of tubular lesions in AKI from 54 individuals with fatal traumatic or toxic injury, using necropsy specimens and mounting and staining of dissected nephrons. In 1979, Solez et al[16] published their report on kidney biopsy specimens from 57 patients with a clinical diagnosis of acute tubular necrosis (ATN) (24 patients with oliguric ATN, 26 with nonoliguric ATN, and 7 in

Table 1. Descriptions of AKI in Selected Reports From the Medical Literature

Authors	Year	Diagnostic Criteria	N	Causes
Abercrombie[3]	1821	Prolonged anuria	5	Not specified but likely: pyelonephritis, abdominal abscess, obstructive uropathy
Bywaters and Beall[7]	1941	Oliguria	4	Rhabdomyolysis from crush syndrome (100%)
Muirhead et al[8]	1948	Oliguria	28	Mismatched blood transfusion (64%), distilled water irrigation for transurethral resection of the prostate (14%), hypotension (14%), carbon tetrachloride toxicity (4%), burns (4%)
Bull et al[9]	1950	Anuria	34	Hemorrhage/ischemia (34%), mismatched blood transfusion (29%), postabortion (24%), nephrotoxins or other (9%)
Swann and Merrill[10]	1953	Oliguria	85	Mismatched blood transfusion (25%), postoperative hemorrhage (21%), distilled water irrigation or infusion (9%), mercury or carbon tetrachloride toxicity (13%), rhabdomyolysis (5%), other miscellaneous (27%)
Hou et al[65]	1983	0.5 mg/dL increase if SCr < 1.9; 1.0 increase if SCr between 2.0 and 4.9; 1.5 increase if SCr $\geq$ 5.0 mg/dL	108	Renal hypoperfusion (42%), surgery (18%), contrast (12%), aminoglycosides (7%)
Leaf et al[19]	2016	KDIGO criteria	100	Ischemic acute tubular necrosis (24%), prerenal azotemia (21%), nephrotoxic acute tubular necrosis (10%), cardiorenal syndrome (8%), glomerulonephritis (5%), obstruction (3%), hepatorenal syndrome (2%), unknown (22%)

Abbreviations: KDIGO, Kidney Disease Improving Global Outcomes; SCr, serum creatinine.