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Expanding the Role for Kidney Biopsies in Acute Kidney Injury

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Abstract

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 leads 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 towards the promise of personalized medicine in nephrology.

Keywords

Acute kidney injury; biopsy; histopathology; pathogenesis

Introduction

In 1950 Homer Smith 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.”¹ In the nearly 70 years since the publication of Smith's 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” through histopathological 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 in order to better

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characterize the lesions and many subendophenotypes that we currently classify as a single entity.

AKI refers to an extremely heterogeneous group of clinical conditions that share common diagnostic features: a rise 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 pre-renal azotemia. Despite the anatomical references to tubules, the interstitium, and the glomeruli inherent in many clinicopathological diagnoses of AKI, kidney biopsies for pathological confirmation and diagnosis are very rarely performed.

The history of diagnosis and descriptions of AKI

As reviewed by Eknoyan in “Emergence of the Concept of Acute Kidney Injury,” the entities we classify as AKI have gone by a multitude of different names.² “Ischuria renalis,” first described by Morgagni and then by Abercrombie,³ indicated suppression or retention of urine (anuric AKI), which was historically 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 pathological findings.⁴ In Osler’s “Textbook of medicine” in 1909, 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*, Homer Smith introduced the term “acute renal failure” and described the available animal and human studies in the literature.¹ The clinical causes of acute renal failure described in Smith’s textbook were shock (hemorrhagic, septic, burns, post-partum), toxins (sulfathiazole chewing gum, carbon tetrachloride), crush syndrome, and intravascular hemolysis.

It is remarkable how different AKI (in the developed world) is today compared to the reports in the 18th through 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 and anti-cancer 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 phases⁵ – is based on reports of the natural history of severe oligoanuric AKI, starting with Bywaters and Beale in 1941 (AKI from crush injuries),⁶ Muirhead et al. in 1948 (AKI from incompatible blood transfusions and other causes),⁷ Bull et al. in 1950 (AKI from multiple causes),⁸ and Swann and Merrill in 1953 (AKI from multiple causes).⁹ Swann and Merrill’s 75 page manuscript, “The Clinical Course of Acute Renal Failure,” describes 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 Swann and Merrill’s report 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 oligoanuric AKI to include the increasingly more common non-oliguric forms. Vertel and Knochel from the US Army Surgical Research Unit, for example, described in a manuscript entitled “Nonoliguric Acute Renal Failure” 11 cases of nonoliguric AKI, 10 of which were from burns, and 14 cases of post-burn oliguric AKI. AKI is now 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 is now estimated to complicate 6% to 20% of hospital admissions, depending on the definition employed.^{10–12}

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. published detailed morphological 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.¹³ In 1979, Solez et al. 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 non-oliguric ATN, and 7 in the recovery phase of ATN) as well as 20 ‘controls’ with normal histopathology who were biopsied for reasons other than AKI.¹⁴ Comparing the tubular lesions across the 57 patients with AKI or recovery, Solez et al. reported that two lesions were less prominent in recovery than in established ATN – necrosis of individual tubular cells and loss of proximal tubule brush border – but that no histopathological differences could differentiate between oliguric vs. non-oliguric ATN, or between AKI from gentamicin vs. without gentamicin. Although the literature on the histopathology of AKI cannot be reviewed here in detail, several notable absences are obvious and have been commented on by others,¹⁵ including: no reports of the histopathology of milder forms of AKI (e.g., pre-renal azotemia, contrast nephropathy); no reports focused on the histopathology of cardiac surgery-associated AKI; and relatively few reports on AKI from sepsis.¹⁶ In short, the reports of the histopathology of human AKI do not adequately reflect the types of AKI treated by clinicians today. Although the reasons are understandable (e.g., safety considerations), the lack of biopsies in human AKI is nevertheless an obstacle to translational research in AKI.

An important point about the phenotype of AKI in the absence of kidney biopsy is the difficulty in assigning causes. Most clinicians taking care of patients with AKI would readily admit that the differential diagnosis of AKI for many patients includes multiple conditions which often co-exist, including ischemia and nephrotoxic exposures, often superimposed on pre-existing chronic kidney disease. In one recent paper describing AKI in hospitalized individuals, 22% of cases were of unknown cause despite manual chart review.¹⁷ Even in the relatively homogenous setting of cardiac surgery associated AKI, Koyner and colleagues reported marked disagreement among three board certified nephrologists who were asked to assign the cause of AKI as pre-renal azotemia or ATN.¹⁸

Clinical Indications for Kidney Biopsy in AKI Today

Only a minority of cases of AKI undergo kidney biopsy. At Brigham and Women's Hospital in the year 2010, for example, 4903 hospitalized individuals met laboratory criteria for AKI, and only 28 underwent kidney biopsy specifically for AKI. Common presentations of AKI that lead to kidney biopsy include suspected glomerulonephritis, coexisting nephrotic syndrome, and unexplained AKI. The Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines for AKI recommend biopsy "if the cause of AKI is not clear after careful evaluation... especially in patients in whom prerenal and postrenal causes of AKI have been excluded, and the cause of intrinsic AKI is unclear... particularly useful when clinical assessment, urinalysis, and laboratory investigation suggest diagnoses other than sepsis, or ischemic or nephrotoxic injury."¹⁹ It should be acknowledged, however, that clinical assessment and laboratory testing for differential diagnosis in AKI suffers from poor sensitivity and poor specificity and is quite underdeveloped.¹⁷ For liver failure, hepatologists use transaminases, bilirubin, alkaline phosphate, and coagulation studies to narrow the diagnostic possibilities for liver disease to specific anatomical sites and/or pathological processes. Tests with pathophysiologic or diagnostic specificity are generally lacking in nephrology for AKI, with the exception perhaps of antineutrophil cytoplasmic antibody and anti-glomerular basement membrane antibody testing in rapidly progressive glomerulonephritis. A number of time honored tests are still taught to medical students for the differential diagnosis of AKI. Fractional excretion of sodium and urinary eosinophils, to take just two examples, have solid physiologic or pathological underpinnings and are used widely, but have unacceptably poor diagnostic performance characteristics when tested rigorously.^{17,20} The urine sediment is often considered a "liquid biopsy,"^{21–23} but the performance characteristics have not been rigorously studied for differential diagnosis in AKI other than pre-renal azotemia vs. ATN.²⁴ Studies on the sensitivity, specificity, and predictive values of the urine sediment for diagnosing acute tubulointerstitial nephritis vs. glomerulonephritis vs. versus ATN have not been performed to our knowledge. Substantial inter-observer variability²⁵ and lack of standardized training for nephrology trainees²⁶ is another major limitation in the reliance on urinary sediment examination over kidney biopsy. An argument for more extensive kidney biopsy in AKI is that widely used and trusted laboratory tests in AKI, including serum creatinine,^{27,28} can be highly misleading.

Deciding to biopsy in AKI

The decision to pursue kidney biopsy in AKI, whether for research or clinical purposes, has to consider the following:

- Is the procedure acceptably safe?
- Does the patient understand the risks and potential benefits of the procedure?
- Will the procedure lead to new knowledge that could change treatment now or in the future:
 - For clinically indicated biopsies: relevant diagnostic or prognostic information

- For research biopsies: research investigations and technologies that have a reasonable chance to advance understanding of AKI

Figure 1 depicts two axes along which clinical decision making must take place: diagnostic uncertainty and therapeutic relevance. The first is to establish clearly the indication for biopsy. Is there diagnostic uncertainty, and second, could resolution of that diagnostic uncertainty lead to a change in clinical management (for treatment in the case of diagnostic uncertainty; or estimation of prognosis in the cases of diagnostic certainty). Cases in which there is great uncertainty and definite therapeutic implications include rapidly progressive glomerulonephritis or unexplained AKI. In some cases, there may be relatively little diagnostic uncertainty but strong therapeutic implications, such as AKI in a patient with known lupus nephritis. In other cases, there may be great diagnostic uncertainty but no therapeutic implications (e.g., contrast nephropathy vs. atheroembolic disease). Not depicted in Figure 1 but of great importance is the safety of kidney biopsy in a given case, discussed later. Clearly, the concept of therapeutic implications for AKI depends on advances in drug development, which in turn arguably requires a better understanding of mechanisms of disease in AKI. Advances in oncology, for example, have been facilitated by research performed over the past few decades on routine biopsies obtained for tissue diagnosis.²⁹

The clinical consequences of not performing biopsies in AKI may be immaterial for patient care, if indeed the presumptive diagnoses are relatively accurate. But in cases where the diagnosis is wrong – for example, the misidentification of ATN as acute interstitial nephritis leading to unnecessary steroid use – the misdiagnosis can result in patient harm from inappropriate use of drugs with serious side effects. Furthermore, the lack of biopsies means that the availability of tissue specimens is limited for research purposes. New diagnostic entities may never come to our attention if biopsies are rarely or never performed for confirmatory diagnosis. Two recent examples from the clinicopathological literature on AKI come to mind. The entities “warfarin nephropathy”³⁰ and “vancomycin crystal nephropathy”³¹ exist only because astute nephrologists, nephropathologists, and laboratory scientists carefully scrutinized pathological case material from clinically indicated biopsies to expand our understanding of potential mechanisms of iatrogenic AKI. In the absence of a kidney biopsy, most clinicians would regard AKI in the context of over-anticoagulation to be due to the other clinical factors that almost always accompany such cases. Similarly, vancomycin toxicity was typically assumed to be from ATN,^{32,33} until careful pathological investigation led to the proposal of intratubular vancomycin crystal formation as a potential mechanism of disease.

Safety of kidney biopsies in AKI

Bleeding is the major risk of a percutaneous kidney biopsy. Interventional radiology guidelines place kidney biopsies in the highest risk category for post-procedure bleeding, along with transjugular intrahepatic portosystemic shunts and biliary interventions.³⁴ Major complications of kidney biopsy have traditionally been defined as need for a blood transfusion, need for intervention to stop bleeding (either surgical or radiologic), urinary tract obstruction and AKI. Minor complications include hematuria, peri-nephric hematomas and the formation of arteriovenous fistulae. Peri-nephric hematomas in particular are very

common, occurring in between 20–86% of cases depending on the timing and modality of the post-biopsy imaging.^{35–38} However, while the absence of a hematoma does appear to be associated with a lower risk of major complications, immediate post-biopsy hematomas are not useful in predicting clinically significant bleeding later.^{39,40} Arteriovenous fistulae occur in approximately 15% of cases and appear to be more common after allograft biopsies. The majority of arteriovenous fistulae resolve spontaneously without intervention although they are occasionally associated with late complications including pain, bleeding and high-output cardiac failure.^{41,42}

The rates of major complications following percutaneous kidney biopsy range from approximately 2–8% in published series.^{38,40,43,44} A large, well done meta-analysis by Corapi et al. of studies of post-biopsy bleeding complications identified a number of independent risk factors. These included the use of larger biopsy needles, lower pre-biopsy hemoglobin, higher baseline serum creatinine, and higher pre-biopsy systolic blood pressure.⁴³ Out of 9474 biopsies included in the study 2 patients died as a result of the biopsy and 1 patient required a nephrectomy due to uncontrolled bleeding. The complication rate in this meta-analysis was lower than that reported in many single center studies, likely due to the inclusion of a small number of large studies with very low complication rates. Publication bias, non-standardized ascertainment policies and definitions for post-biopsy complications, and differing thresholds for blood transfusion or interventional procedures should be kept in mind when comparing reports across centers to the published literature.

Kidney biopsies for AKI are inherently higher risk than biopsies for other indications, because of concomitant uremia, anemia, and the often urgent need for biopsy. In studies that include information on the reason for biopsy, AKI is associated with a two- to seven-fold increased risk of major bleeding complications (Table 2). In the meta-analysis by Corapi et al, for example, studies in which >10% of participants had a biopsy for AKI had a higher rate of blood transfusion.⁴³ A large registry study of all patients undergoing kidney biopsy in Norway over a 20-year period included more than 9000 biopsies. Of these, 18% were performed for AKI. In the unadjusted analysis, AKI was associated with a two-fold increase in the risk of bleeding. However, this risk disappeared after adjustment for age and eGFR category at the time of biopsy,⁴⁰ suggesting that the risk of bleeding may be more related to the level of kidney dysfunction rather than the AKI itself. Patients with AKI may be more likely to have a biopsy while still receiving anti-platelet agents due to the relatively urgent nature of the biopsies. A retrospective review of complication rates in two Scottish hospitals, one of which stopped aspirin and the other which continued through the time of biopsy, found that there was no difference in major bleeding complications when aspirin was continued. However, there was a significantly higher risk of minor bleeding complications including a fall in hemoglobin of > 1g/dl. The rate of major bleeding complications was 7-fold higher in patients undergoing an emergent biopsy compared with elective biopsies (3.7 vs 0.5%, $p<0.001$).⁴⁵ The risk of major complications following percutaneous kidney biopsy is particularly high in patients in the intensive care unit (ICU). Whether the excess risk of biopsies in the ICU is due to case-mix (e.g., more biopsies for specific indications such as rapidly progressive glomerulonephritis or vasculitis compared with the non-ICU population) has not been well studied. A recent study of 56 biopsies for AKI in the ICU reported a 12.5% rate of major complications and one death directly as a result of the biopsy.⁴⁶

Another retrospective study of 77 patients biopsied for AKI in the ICU reported a complication rate of 22%, with 11% of patients requiring embolization or the transfusion of >3 units of red cells in the 48 hours following the biopsy.⁴⁷ Thus, it appears that ICU patients are a particularly high risk population and that research-only biopsies should be avoided in the ICU.

Research biopsies with an extra “core” or pass

In clinically indicated biopsies, additional tissue for research can be obtained from an additional pass of the biopsy needle for a research core. Intuitively, repeat biopsy passes should be associated with a higher risk of bleeding. To our knowledge, no study in the published literature has shown that the number of passes of the biopsy needle is associated with a higher risk of major complications. There is a clear bias in observational analyses, however, that should be acknowledged: multiple passes may not be performed in certain patients with technically difficult biopsies, or in patients who have a hematoma following the first or second pass. The observation that multiple passes are not associated with higher rates of bleeding complications could therefore be biased from confounding by indication⁴⁸ (i.e., extra passes are more likely to be done in those at lower risk of bleeding). Whether an extra core biopsy on top of clinically indicated biopsies is truly safe (i.e., is associated with *no excess risk*) has not in our opinion been demonstrated, but could be studied by comparing bleeding rates in research biopsy studies involving an extra pass compared to historical complication rates. Kidney biopsy research cores have been obtained in a number of studies involving diabetes, nephrotic syndrome, and Fabry disease; comparing post-biopsy bleeding rates and hemoglobin levels in these studies would be informative, though not necessarily generalizable to research biopsies in AKI.

Alternative approaches for obtaining human kidney tissue to study AKI

Some forms of AKI that are of particular scientific and clinical interest, for example AKI in multiple organ dysfunction syndrome, septic shock, or following cardiac surgery, occur in patients who are at high risk for kidney biopsy due to coagulopathy, hypotension, thrombocytopenia, or concomitant use of aspirin, antiplatelet agents, or other anticoagulants. A large proportion of hospitalized AKI may therefore be ineligible to participate – or difficult to recruit, due to physician reluctance (see Table 4) or patient reluctance. Another potential source of kidney tissue from critically ill patients is postmortem exams. A number of pathology departments around the country and world have developed what are called “rapid autopsy” programs.^{49–52} These programs have primarily focused on oncology, for the collection of tumor samples from distant metastases or other sites when biopsies cannot be performed safely during life. Neuropathologists have also obtained brain tissue post-mortem for the study of Alzheimer’s disease.⁵³ The Genotype-Tissue Expression (GTEx) Project, sponsored by the NIH Common Fund, has established an infrastructure for biospecimen procurement for prospective collection of organ tissues from autopsy specimens.⁵⁴ To minimize the effects of autolysis due to the length of the post-mortem interval, the GTEx project made an effort to collect samples within 8h of death. For the purpose of kidney tissue, that time interval is too long. Investigators at Washington University also performed rapid procurement of kidney (and heart) tissue harvesting via limited bedside autopsy 30

min to 3 hours postmortem to study mechanisms of cardiac and renal dysfunction in patients dying of sepsis.¹⁶

Kidney tissue can be obtained through a number of approaches beyond percutaneous biopsy: surgical biopsies during laparotomy or laparoscopy, during nephrectomy, during urologic procedures, at autopsy, and through a transjugular approach (Table 3). Each has limitations related to safety, suitability of tissue specimens, and patient selection. Percutaneous biopsy also has a major limitation in that primarily cortex is sampled, leaving the medulla as a “black box.” Finally, biopsy specimens may not provide insight into regional perfusion abnormalities. A comprehensive study of human AKI will need to involve not just human tissue but also novel imaging modalities, biomarker investigations, and representation of non-cortical tissue.

Ethics of research kidney biopsies in AKI

Advances in AKI research will depend on the availability of human kidney tissue specimens, which will require physicians to ask their patients to accept a non-negligible risk of harm in return for the possibility of benefit to themselves or to society. The relevant ethical principles include autonomy, nonmaleficence, beneficence, and justice. For research biopsies, ensuring that informed consent is truly well informed is critical. Clearly articulating to our professional colleagues and to our patients (or prospective study subjects) the indication for biopsy is also important, because thresholds for acceptable risk depend on the purpose of the biopsy (i.e., pure research biopsy in a setting such as pre-renal azotemia versus an extra core in a patient with AKI of unexplained cause undergoing a clinically indicated biopsy). Given the complexity of clinical decision making in AKI, the necessarily subjective nature of deciding whether to biopsy for an individual case, and the risks involved, involving multiple stakeholders will be critical for the field before embarking on research biopsies. The distinction between “clinically indicated” and “research” biopsies – and conveying this distinction to patients, payors, and professional colleagues – is challenging, especially as indications for biopsy may evolve over time as new information is gained.

Survey of physician attitudes towards research kidney biopsies for AKI

In October 2016 we sent an IRB-approved, anonymous, internet-based survey request to 60 hospitalists and 98 nephrologists at the three academic teaching in Boston. The response rate was 25% for hospitalists and 58% for nephrologists (total N = 71). 24% of respondents were primarily clinical, 24% were primarily research, and 53% had a mix of clinical, administrative, and research roles. All but 2 of the nephrologists and none of the hospitalists had previously performed at least one kidney biopsy. 31% had performed more than 50 biopsies. Each respondent was given several questions and hypothetical AKI cases and asked whether they would permit a patient to be approached for participation in the following contexts: 1) an additional pass for a research specimen in clinically indicated biopsies; 2) research biopsies in cases that are not usually biopsied but have some clinical equipoise (e.g., allergic interstitial nephritis vs. ATN); and 3) purely research biopsies in cases with no clinical equipoise (e.g., ATN following cardiac surgery). The results are shown in Table 4.

For clinically indicated biopsies, no physician responded with “Absolutely Not” or “Unlikely” to the question about reserving a portion of the kidney tissue for research, but 8.6% reported that they would “Absolutely Not” allow an extra pass. Physicians were substantially more willing to allow research biopsies in cases of clinical equipoise, where the biopsy could provide clinically relevant information even if it was not clinically indicated. Responses were “Likely” or “Definitely Yes” in 52.8% for the question involving AIN vs. ATN from hypotension, 36.2% for contrast nephropathy vs. atheroemboli, and 40.3% for post-cardiac surgery ATN vs. AIN. In cases without clinical equipoise, responses were “Absolutely not” or “Unlikely” in 42.9% for the question involving clear-cut AIN, 63.7% for contrast nephropathy, and 62.3% for post-cardiac surgery ATN. This small survey from the northeast United States provides preliminary evidence of the diversity of viewpoints even among clinicians regarding the ethics of research biopsies in AKI. One clear signal was that some possibility of direct benefit to the patient participant would be an important criterion for research kidney biopsies. Eliciting perspectives from patients and members of diverse communities on these questions will be critical.

Research biopsies in other contexts

An example of research biopsies in other disease settings is diffuse intrinsic pontine glioma (DIPG), a devastating and rapidly fatal pediatric brain cancer that was once considered contraindicated for biopsy because of procedural risks, dismal prognosis, and the ability to make a clinical diagnosis non-invasively through MRI.^{55–57} Now, in the context of clinical trials in which tissue will be used for research and to investigate biological markers for rational selection of treatment options, surgical biopsy for DIPG is ethically justifiable and included in randomized controlled trials (e.g., NCT01182350, NCT02233049). In nephrology, research biopsies in the absence of a clinical indication for CKD have been performed in diabetic nephropathy,^{58,59} hypertensive kidney disease,⁶⁰ and Fabry disease.⁶¹ Lessons for AKI investigators from experiences in oncology⁶² and CKD should prove invaluable in the design and conduct of biopsy studies.

Summary

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 leads 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 towards the promise of personalized medicine in nephrology.

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Therapeutic Relevance

DIAGNOSTIC UNCERTAINTY

Figure 1. Clinical decision making for kidney biopsies in acute kidney injury

Clinicians weigh diagnostic uncertainty and potential therapeutic relevance when deciding whether to perform a diagnostic kidney biopsy in patients with AKI. Cases with high diagnostic uncertainty and high therapeutic relevance such as rapidly progressive glomerulonephritis (upper right box) are most likely to undergo biopsy. Cases with little diagnostic uncertainty and little therapeutic relevance such as contrast nephropathy are unlikely to undergo biopsy. The decision to biopsy patients with suspected acute interstitial nephritis vs. acute tubular necrosis is high variable. Abbreviations: AIN, acute interstitial nephritis; ATN, acute tubular necrosis; RPGN, rapidly progressive glomerulonephritis.

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 ⁶	1941	Oliguria	4	Rhabdomyolysis from crush syndrome (100%)
Muirhead ⁷	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 ⁸	1950	Anuria	34	Hemorrhage/ischemia (34%); mismatched blood transfusion (29%); post-abortion (24%); nephrotoxins or other (9%)
Swann and Merrill ⁹	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 ⁶³	1983	0.5 mg/dL increase if SCr < 1.9; 1.0 increase if between 2.0 and 4.9; 1.5 increase if > 5.0 mg/dL	108	Renal hypoperfusion (42%); surgery 18%; contrast 12%; aminoglycosides 7%
Leaf ¹⁷	2016	KDIGO criteria	100	Ischemic acute tubular necrosis 24%; pre-renal 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.

Table 2

Studies reporting major complication rates following native kidney biopsy for acute kidney injury.

Study	Total n	Overall rate of major complications, %	Acute kidney injury, n (%)	Findings
Tondel 2012 ⁴⁰	9288	0.9%	1723 (18.6)	Odds ratio for major complication 2.29 (1.50–3.6) with biopsy for AKI vs others reasons. After adjustment for baseline estimated glomerular filtration rate, no difference: odds ratio 1.1 (0.63–1.80)
MacKinnon 2008 ⁴⁵	1120	1.9%	AKI: 281 (25) Emergent: 637 (56.9)	Significantly higher risk of major complications (3.7 vs. 0.5%, $p<0.001$) in patients undergoing an emergent biopsy. No analysis of AKI vs. no AKI. Greater risk of minor complications in patients who continued anti-platelet agents (31% vs. 11.7%)
Corapi 2012 ⁴³	4110	1.9%	Unclear	Studies including a higher proportion of patients with AKI (>10%) had a higher rate blood transfusion (1.1 vs. 0.04%, $p<0.001$)
Korbet 2012 ⁴⁴	1055	6.6%	Unknown	No information but markedly higher rate of complications in patients with high creatinine at baseline (OR 1.8, 95%CI 1.2–2.9, $p=0.009$)
Gonzalez 2000 ⁶⁴	1005	2.4%	Unknown	OR 4.03 for major complications in patients undergoing a renal biopsy for AKI vs. other reasons.

Table 3

Alternatives to percutaneous kidney biopsy for research specimens in human acute kidney injury.

Source of tissue	Example in the literature	Limitations
Rapid post-mortem biopsy	Takasu 2013 ¹⁶	Autolysis after death; informed consent of family, logistics, and acceptability to providers
Transjugular biopsy	(numerous)	Unclear if lower risk than percutaneous biopsy
Intraoperative biopsy during laparotomy	(numerous)	Limited to those undergoing laparotomy
Procedural biopsies during urological procedures	Linnes 2013 ⁶⁵	Limited to those undergoing nephrolithotomy; access mainly to papillae and not cortex
Intraoperative biopsy during nephrectomy	Parekh 2013 ⁶⁶	Unclear relevance of ischemia to most cases of AKI
Deceased donor biopsy	Kruger 2009 ⁶⁷	Unclear relevance to most cases of AKI

Table 4

Clinician attitudes towards obtaining kidney tissue for research.

	Absolutely Not	Unlikely	Maybe	Likely	Definitely Yes
For clinically indicated biopsies					
Reserve a small portion of an existing core	0	0	1.5	25	73.3
Perform an extra pass to obtain an extra core	8.9	22.1	36.8	19.1	13.2
Willingness to perform a research biopsy					
In cases of clinical equipoise					
Suspected AIN vs. ATN from hypotension	7.4	13.2	27.9	35.3	16.2
Suspected contrast nephropathy vs. atheroemboli	4.5	34.4	26.9	25.4	9
Suspected post-cardiac surgery ATN vs. AIN	3	23.9	32.8	28.4	11.9
In cases without clinical equipoise					
Acute interstitial nephritis	8.8	33.8	25	20.6	11.8
Contrast nephropathy	11.9	52.2	13.4	16.4	6
Post-cardiac surgery ATN	16.4	46.3	14.9	16.4	6

Responses by 71 clinicians to an internet-based survey are shown below as percentages. Abbreviations: AIN, acute interstitial nephritis; ATN, acute tubular necrosis.