Update on the Native Kidney Biopsy: Core Curriculum 2019

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The kidney biopsy is an invaluable tool that has become the gold standard for the diagnosis of pathologic kidney diseases since the early 1950s. Throughout the years, immunohistologic and ultrastructural microscopy techniques have improved and provide more information on the cause and classification of kidney diseases than that available from simple light microscopy alone. Kidney biopsy has become a preferred method to obtain critical information that can be used in conjunction with serologic, urinary, and genetic testing to diagnose a variety of kidney diseases, both acute and chronic. The kidney biopsy procedure carries relatively low risk and yields substantial information. Potential complications include bleeding requiring transfusion, gross hematuria, arteriovenous fistula formation, and perinephric hematoma, among others. Percutaneous kidney biopsies are typically performed using real-time ultrasound or computed tomographic imaging. This Core Curriculum briefly outlines the history of the kidney biopsy, then discusses indications, complications, and specific procedural aspects.

Complete author and article information provided before references.

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History of the Kidney Biopsy

The microscopic assessment of histopathologic lesions in kidney biopsy tissue was predated by macroscopic examination of kidney tissue at the time of autopsy. In the 19th century, with the invention of the microtome, autopsy reports started including renal histology on unstained specimens. With the introduction in the late 19th and early 20th centuries of various specific stains (derivatives of which are still used today), the evaluation of autopsy kidney specimens became more thorough and detailed.

The first surgical biopsy of the kidney was performed by Dr George Edelbohls as part of a renal-capsule stripping technique in patients with Bright disease. These early histologic descriptions included "pronounced changes in the interstitial tissue and glomeruli, the latter having in many instances undergone fibrosis and hyaline degeneration." Through the early to mid 20th century, surgical kidney biopsy grew in popularity.

The percutaneous kidney biopsy was first realized, rather coincidentally, when kidney tissue was accidently obtained during liver biopsies. The first true aspiration needle biopsy of the kidney was performed by Nils Alwall in 1944 using x-ray and retrograde pyelography. The kidney biopsy was then mostly used for the diagnosis of renal neoplasms. The percutaneous kidney biopsy by aspiration technique was perfected by other physicians and brought to the forefront of diagnostic tools in nephrology by Poul Iverson and Claus Brun in a landmark publication in the *American Journal of Medicine* in 1951. The biopsy was seen as a safe way to have a meaningful impact on diagnosis, with an early analysis by Robert Kark showing that the diagnosis was altered in 25 of 48 patients undergoing biopsy. With the advent of newer diagnostic stains and microscopic techniques, including immunofluorescence and scanning electron microscopy, the field of renal pathology began to flourish as a subspecialty of surgical pathology.

Although historically nephrologists performed most kidney biopsies, currently a significant fraction are performed by physicians other than nephrologists, typically radiologists. Data collected within the last 10 years have shown that although nephrology training programs offer opportunities to acquire the required kidney biopsy skills, many graduating nephrology fellows do not feel competent to perform kidney biopsies on their own in practice. The trend toward having radiologists perform kidney biopsies likely reflects time and reimbursement constraints. Nonetheless, competence in performance of kidney biopsies, both native and transplant, is a required element of nephrology fellowship training.

Additional Readings

- Berns JS. A survey-based evaluation of self-perceived competency after nephrology fellowship training. *Clin J Am Soc Nephrol.* 2010;5(3):490-496. ★ **ESSENTIAL READING**
- Berns JS, O'Neill WC. Performance of procedures by nephrologists and nephrology fellows at U.S. nephrology training programs. *Clin J Am Soc Nephrol.* 2008;3(4):941-947.

The Core Curriculum aims to give trainees in nephrology a strong knowledge base in core topics in the specialty by providing an overview of the topic and citing key references, including the foundational literature that led to current clinical approaches.

- Cameron JS, Hicks J. The introduction of renal biopsy into nephrology from 1901 to 1961: a paradigm of the forming of nephrology by technology. *Am J Nephrol.* 1997;17(3-4):347-358.
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Indications for Kidney Biopsy

Case 1: *A 53-year-old man with a history of type 2 diabetes mellitus for 10 years without signs of retinopathy or neuropathy and also hypertension for 5 years controlled with atenolol, 50 mg, daily and lisinopril, 10 mg, daily is presenting for evaluation of moderate lower-extremity edema. Blood pressure is 134/76 mm Hg with a heart rate of 74 beats/min, with examination findings notable for bilateral pretibial edema (1+). Laboratory test results are relatively unremarkable, with a serum creatinine (Scr) level of 1.09 mg/dL (stable for the last 3 years), with the exception of serum albumin level of 2.5 g/dL (normal 3 years prior) and urine albumin-creatinine ratio (UACR) of 4,775 μg/mg, which is higher than that from 1 year ago (when it was 185 μg/mg). Urine sediment demonstrates 5 to 10 red blood cells per high-power field, with 5% dysmorphic red blood cells.*

Question 1: Based on this presentation, what is the best next step in the management of this patient?

a) Reassess UACR in 1 month
b) Increase lisinopril dosage
c) Initiate treatment with corticosteroids
d) Proceed with kidney biopsy

For the answer to the question, see the following text.

The kidney biopsy is an invasive procedure with potential risks. A kidney biopsy should be recommended when kidney tissue is required to make a definitive diagnosis that might affect treatment or provide information about disease progression or prognosis. A biopsy should be avoided when the potential risk to the patient exceeds any likely benefit from procuring kidney tissue.

A biopsy should be contemplated for certain patients with acute kidney injury (AKI), proteinuria, or hematuria (Table 1). However, not every such patient requires a kidney biopsy. Patients with AKI due to decreased kidney perfusion or obstruction need not undergo a kidney biopsy unless the initial cause for injury has been corrected and there is still confusion regarding the cause of AKI. Patients with intrinsic AKI may have tubulointerstitial disease, vascular disease, or glomerular disease. Patients with a diagnosis of hemodynamically mediated AKI (acute tubular injury or necrosis) do not usually need a biopsy unless the cause of the AKI is unclear or there are other features that suggest a need for a biopsy, such as new proteinuria or hematuria. In patients with possible acute interstitial nephritis, a biopsy may be necessary if there is ambiguity in the diagnosis or if necessary before initiating immunosuppression treatment with glucocorticoids.

Table 1. Indications for Kidney Biopsy

Indications	Comments
Hematuria	Presence of acanthocytes or red blood cell casts with an elevated Scr level or proteinuria
Proteinuria	Proteinuria > 1 g/d as measured on multiple visits with no clear comorbidity; proteinuria > 3 g/d in the absence of diabetes or a rapid increase in proteinuria even with diabetes; proteinuria < 3 g/d with an elevated Scr level with no clear comorbid conditions such as diabetes or hypertension
AKI	In the setting of ATI, persistent injury despite reversal of cause or if Scr did not return to baseline with 7-14 d of injury onset; in the setting of presumptive AIN, if there has been no resolution of injury despite removal of culprit medication
CKD	Rapid elevation in Scr level or new-onset hematuria or proteinuria

Abbreviations: AIN, acute interstitial nephritis; AKI, acute kidney injury; ATI, acute tubular injury; CKD, chronic kidney disease; Scr, serum creatinine.

The presence of new-onset proteinuria or proteinuria accompanied by hematuria is often an indication for kidney biopsy to assess for and diagnose glomerular disease and guide therapy. Patients with low-grade proteinuria (protein excretion < 0.5-1 g/d) may not require a biopsy unless there is an accompanying elevated Scr level, hematuria, or evidence of a systemic disease (such as systemic lupus erythematosus). In diabetic patients with new onset of nephrotic-range proteinuria without antecedent proteinuria, a biopsy should generally be performed because such patients often have a lesion other than any underlying diabetic kidney disease.

Patients with isolated hematuria with normal estimated glomerular filtration rates without proteinuria, in whom other nonkidney diseases of the genitourinary tract have been excluded, may not require a biopsy. These patients will most often have nonproteinuric immunoglobulin A (IgA) nephropathy or thin basement membrane disease. The course of such patients is usually benign with excellent prognosis unless proteinuria or a worsening estimated glomerular filtration rate develops, at which time a biopsy could be considered. Hematuria in the presence of proteinuria and elevated Scr level generally requires a biopsy to make a diagnosis.

Patients with known or suspected systemic lupus erythematosus or other glomerular diseases who present with hematuria or proteinuria with or without an elevated Scr level should generally undergo biopsy to

classify the specific glomerular lesion and guide subsequent therapy. In addition, patients with previously biopsied lupus nephritis may also benefit from a later repeat biopsy to assess kidney disease activity and guide therapy.

In case 1, this patient with diabetes has not had evidence of significant proteinuria in the recent past. The sudden onset of nephrotic-range proteinuria in a patient with diabetes should be evaluated with a kidney biopsy. Empirically treating the patient with corticosteroids would not be advised because without a diagnosis, the therapy is unclear and corticosteroids may elevate blood glucose level significantly. Titration of his lisinopril dosage would not be enough if this were nondiabetic glomerular disease. Thus, the best answer is (d).

Additional Readings

- Hogan JJ, Mocanu M, Berns JS. The native kidney biopsy: update and evidence for best practice. *Clin J Am Soc Nephrol.* 2016;11(2):354-362. ★ ESSENTIAL READING
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Contraindications to Kidney Biopsy

Case 2: *A 43-year-old woman with a history of chronic hypertension and a congenitally solitary kidney is presenting for evaluation of new-onset proteinuria. Her blood pressure is treated with hydrochlorothiazide and lisinopril. Examination demonstrates blood pressure of 138/72 mm Hg and she has lower-leg edema (2+). Scr level is stable at 1.4 mg/dL and UACR is 6,835 mg/g, higher than that from 6 months ago (when it was 108 mg/g).*

Question 2: Based on this presentation, what is the best next step in the management of this patient?

a) Refer to surgery for an open surgical kidney biopsy
b) Proceed with a percutaneous kidney biopsy
c) Empirically treat with corticosteroids
d) Increase lisinopril dose and monitor

For the answer to the question, see the following text.

The kidney biopsy is a procedure that comes with risk, most notably bleeding. Contraindications to kidney biopsy are associated with patient characteristics that increase the risk for significant postprocedure bleeding (Table 2). Patients undergoing an elective biopsy with uncontrolled hypertension who cannot be managed with intravenous or oral medications should have the biopsy delayed. Patients undergoing an emergent biopsy in whom blood pressure cannot be appropriately controlled may benefit from a surgical biopsy or interventional transjugular biopsy, in which extracapsular bleeding can be intervened upon.

The use of anticoagulation agents also increases the risks of a kidney biopsy. Patients on long-term anticoagulation therapy may undergo a biopsy if it is safe to withhold the anticoagulation treatment for a sufficient time for reversal of the anticoagulant effect and some time afterward. Patients who are on warfarin or direct-acting factor Xa inhibitor therapy should withhold the anticoagulant for at least 72 hours hours before the biopsy, depending on pharmacokinetics and

Table 2. Contraindications to Kidney Biopsy

Contraindication	Comment
Bleeding risk	Increased bleeding risk with platelet count < 120 × 10^3/μL, elevated INR, and use of anticoagulation including aspirin, warfarin, heparin, and direct factor Xa inhibitors
Anticoagulation concerns	Higher risks would exist in patients in whom stopping anticoagulation therapy would pose significant medical risk (mechanical valve, active VTE disease, high $CHADS_2$ score, LVAD, active APLS)
Hypertension	If systolic BP > 140 mm Hg, BP should be lowered before proceeding
Small hyperechoic kidneys	Indicative of chronic disease and should be avoided if eGFR is < 30 mL/min/1.73 m^2
Anatomical kidney problems	Vascularity of kidney anomalies or multiple cysts increase bleeding risk
Horseshoe kidney	Preferred route is transjugular biopsy
Multiple bilateral cysts	If cysts are numerous, it may be difficult to visualize areas that are cyst free
Hydronephrosis	Biopsy should be delayed until the obstruction is relieved and only pursued if injury persists despite adequate time
Solitary kidney	If the kidney is visible and biopsy is safe, there is no increased risk with a solitary kidney performed by an experienced provider
Infection	Skin infection over the site of needle insertion can lead to sepsis; ongoing pyelonephritis could worsen infection and lead to sepsis
Altered mental status	If the patient cannot cooperate with the biopsy, the risk for injury may be too significant

Abbreviations and definitions: APLS, antiphospholipid syndrome; BP, blood pressure; $CHADS_2$, congestive heart failure, hypertension, age (≥65 years = 1 point, ≥75 years = 2 points), diabetes, and stroke/transient ischemic attack (2 points); eGFR, estimated glomerular filtration rate; INR, international normalized ratio; LVAD, left ventricular assist device; VTE, venothromboembolic.

the patient's underlying thromboembolic risk. If necessary, a short-acting injectable form of low-molecular-weight heparin, or for inpatients, standard heparin intravenously, can be used up until 8 to 12 hours before biopsy. If patients need an urgent biopsy and are on warfarin therapy with an elevated international normalized ratio (INR), either vitamin K or fresh frozen plasma can be administered to acutely reverse the INR. Resuming anticoagulation therapy should occur no sooner than 12 hours after the biopsy and preferably 48 to 72 hours after the biopsy, weighing risks for bleeding and thromboembolism. In patients with underlying bleeding diathesis, whether acquired or genetic, biopsy should be avoided unless the bleeding disorder can be safely reversed and managed immediately postbiopsy.

Antiplatelet agents, including aspirin, clopidogrel, and prasugrel, also confer increased risk for bleeding. Standard practice is to withhold these agents for 7 days before the procedure. However, no study has demonstrated a significantly decreased risk for bleeding complication when this is followed. There may be an increased risk for minor, but not major, bleeding, if these drugs are not withheld before the biopsy.

The presence of small hyperechoic kidneys generally suggests irreversible advanced chronic kidney disease. Pursuing a biopsy in such patients will most likely not yield clinically meaningful data and thus is usually avoided. A horseshoe kidney or kidneys with multiple large renal cysts or tumors should be approached with caution because the vascular anatomy of these kidneys may be misleading. Doppler duplex ultrasound may be useful in assessing this, and alternative biopsy approaches should be considered. Patients with hydronephrosis should not undergo biopsy until the obstructive process can be reversed. A solitary kidney (or single functioning kidney) can be biopsied safely with a percutaneous approach by an experienced provider because the risk for complications leading to serious injury requiring nephrectomy is low. However, if nephrectomy is required, the patient will be left functionally anephric.

Two absolute contraindications include patients who have an active kidney infection or skin infection at the site of needle insertion because the risk for sepsis is increased in these circumstances. In addition, if the patient cannot cooperate with the biopsy due to cognitive impairment, psychiatric disease, or other alterations in mentation, a percutaneous biopsy should not be performed.

In case 2, the patient has new-onset nephrotic syndrome and should proceed with a kidney biopsy. The patient has a solitary kidney, but this should not be a contraindication to biopsy assuming that risks are managed with adequate blood pressure control and, if possible, temporarily withholding anticoagulation therapy. Thus, the best answer is (b); however, the biopsy should be performed by an experienced proceduralist.

Special Patient Populations

Pregnant Patients

Case 3: *A 27-year-old woman who is at 16 weeks' gestation is presenting with mildly elevated blood pressure at 138/86 mm Hg, a facial rash, and lower-extremity edema that have been present for the last 9 days. Scr level is 1.4 mg/dL (baseline at beginning of pregnancy of 0.8 mg/dL) and UPCR is 3,651 μg/mg, which is new in onset since the beginning of pregnancy. At the time of consult, antinuclear antibody test results are pending, C3 level is 82 mg/dL, and C4 level is 16 mg/dL.*

Question 3: Based on this presentation, what is the best next step in management of this patient?

a) Start patient on empirical corticosteroid therapy for new-onset lupus nephritis
b) Proceed with a computed tomography (CT)-guided percutaneous biopsy
c) Proceed with an ultrasound-guided percutaneous kidney biopsy
d) Start the patient on lisinopril therapy to help control blood pressure and proteinuria

For the answer to the question, see the following text.

Kidney disease in pregnancy can present with either proteinuria or hematuria or an acute increase in Scr level. The time relationship of AKI patterns in pregnancy allows for probable diagnosis based on history, timing of symptom onset, and hematologic and serologic evaluations. Biopsies in pregnant patients are generally safe, with studies showing a low complication risk before 20 weeks' gestation and case reports showing on average a 2-fold increase in bleeding after 20 to 25 weeks' gestation. Ideally, the pregnant patient should undergo a percutaneous ultrasound-guided kidney biopsy because CT-guided and transjugular biopsies involve radiation exposure. The technique is similar to that for the nonpregnant patient with the exception of positioning favoring the lateral decubitus or sitting upright position as opposed to the prone position after the 20th week of pregnancy.

In case 3, the patient has AKI, hypertension, proteinuria, and a facial rash, suggestive of systemic lupus erythematosus. She should undergo a percutaneous biopsy. Ultrasonography should be used because CT exposes the developing baby to unnecessary radiation. Empirical glucocorticoid therapy should be avoided until the biopsy is complete. Lisinopril should never be used in a pregnant patient. Thus, the best answer is (c).

Cirrhotic Patients

Patients with cirrhosis are at risk for developing AKI or disease. The patient with liver failure may present with significant bleeding risk due to a low platelet count or coagulopathy and elevated INR. Cirrhotic patients appear to have increased risk for postbiopsy bleeding. However, if a percutaneous biopsy is necessary due to lack of

interventional expertise, a single pass yielding 1 core can be obtained and used for light microscopy, immunohistochemistry, and electron microscopy, thereby minimizing the risk for bleeding in this cohort of patients in which risk for bleeding has not been fully realized.

Other Select Patient Populations

Mechanical ventilation leads to positional challenges, with the patient needing to be prone while intubated, sitting upright, or placed in the right lateral decubitus position. Timing of sample acquisition can be adequately achieved with an inspiratory or expiratory hold with the ventilator. Patients with ventricular assist devices require near-constant anticoagulation therapy and therefore withholding anticoagulation in these patients introduces considerable risk.

Additional Readings

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The Biopsy Technique

Maintaining Sterility

The risk for infection is minimal because the kidney biopsy is performed under sterile conditions. Estimated infection risks are reported to be as low as 0.2%. It can be increased in patients who have an underlying kidney infection or who are immunocompromised. Avoiding cutaneous areas that show signs of infection can help minimize this risk. Proper sterile technique should be maintained throughout the entire procedure by the physician performing the biopsy and, if applicable, by the ultrasonography operator.

Managing Blood Pressure

Blood pressure control is important when performing a kidney biopsy. A recent study of 293 patients undergoing kidney biopsy demonstrated a more than 10-fold increase in biopsy complication risk when systolic blood pressure was > 140 mm Hg and diastolic blood pressure was > 90 mm Hg. The risk for complications was further increased in patients who had blood pressure > 170 mm Hg (with an odds ratio of 23.3). Therefore, efforts should be made to decrease the blood pressure with either intravenous or oral antihypertensives before the biopsy. Oral blood pressure medications can be used, especially if the biopsy is nonurgent. Blood pressure should also be monitored immediately after the biopsy, with efforts to keep blood pressure < 140/90 mm Hg. In the postprocedure period, an elevated blood pressure that is refractory to treatment may be suggestive of a capsular hematoma and should warrant repeat imaging (see below for complications).

Bleeding Risk

Given the vascularity of the kidney, bleeding is a substantial risk in patients undergoing kidney biopsy and efforts should be made to mitigate this risk. Uremia, thrombocytopenia, and coagulopathies increase the risk for bleeding. As platelet levels decrease to $<200 \times 10^3/\mu L$, there is an incremental increased risk for bleeding, with more significant bleeding occurring when platelets decrease to $<120 \times 10^3/\mu L$. In patients with platelet levels < 80 to $100 \times 10^3/\mu L$, platelet transfusions can be used to bring platelet counts closer to normal if the operator believes it is necessary. An elevated INR should be reversed with vitamin K or fresh frozen plasma to help reduce the risk for bleeding, although the exact target has not been appropriately defined. Desmopressin (dose of 0.3 μg/kg) administered 1 half-hour before biopsy has also been recommended in patients with azotemia. A randomized study of 162 adults demonstrated decreased bleeding in patients using desmopressin relative to those assigned placebo. However, this study included patients with Scr levels of 1.5 mg/dL and estimated glomerular filtration rates > 60 mL/min/1.73 m^2. Therefore, the utility of desmopressin in high-risk patients is unclear. After the procedure, the patient should remain supine for 4 to 6 hours. Overnight stay has not been shown to be more beneficial in reducing bleeding risks relative to those who are monitored for up to 6 hours. Although a third of complications still occur at more than 8 hours after the procedure, observation will identify a decrease in hemoglobin level and possibly result in increased transfusions, but it is unclear whether a longer stay will improve post-biopsy outcomes. The choice of an overnight observation should be at discretion of the physician performing the biopsy after accounting for all risks.

Biopsy Methods

Ultrasound- and CT-guided biopsies are performed with the patient in the prone position. Patients who cannot remain prone (due to immobility issues, abdominal distension or ascites, or intubation) should be positioned in the lateral decubitus or sitting position. Once prone, the patient may require support under the abdomen to help elevate the kidney closer to the surface of the back. The choice of ultrasonography or CT as a modality is largely dependent on the nephrologist's comfort with the given technology.

Percutaneous ultrasound-guided kidney biopsy is usually performed on the inferior pole of the left or right kidney. The left kidney is visible without other organs impeding acquisition of the tissue; however, in the case of splenomegaly, injury to the spleen can be significant. The right kidney sits partially under the liver and this position may obstruct a path to the kidney. Ultimately, choice of kidney should be made after adequately assessing potential

paths for both kidneys. Upon visualization with ultrasonography, there should be no bowel close to the inferior pole of the kidney. If bowel obscures the path, the operator should attempt a biopsy on the contralateral kidney or abort the procedure. During the ultrasound examination, blood flow to the kidney should be evaluated, which serves 2 purposes. First, it will determine whether there is adequate flow to all poles of the kidney (absent flow in the pole of intended biopsy may suggest a prior renal infarct, thereby making yield from that particular area low). Second, it will give the provider an estimate of vascularity in the area. Areas with more significant flow should be avoided to minimize bleeding risks. Under local anesthesia (such as lidocaine), the needle is advanced with direct visualization using ultrasonography and observed entering the kidney (Fig 1A). Based on the provider, a trocar or needle guide may be used with this technique.

The CT-guided biopsy is similar to an ultrasound-guided biopsy except the patient is not visualized in real time. Instead, CT is used to mark and measure the distance from the skin to the kidney capsule. A trocar is then inserted and the patient is reimaged to confirm that the trocar tip is abutting the kidney capsule (Fig 1B). Samples are then obtained without direct visualization. CT-guided biopsies allow for a more accurate localization of the kidney relative to the ultrasonography device and are often preferred in obese patients who may have deep or difficult-to-visualize kidneys or patients with cysts. However, CT use comes with radiation exposure.

If a percutaneous biopsy is not possible for any of the relative contraindications indicated and a biopsy is still necessary, it is possible to undergo a transjugular biopsy by an interventional radiologist or an open or laprasopic surgical biopsy. The transjugular biopsy allows for direct venous access to the kidney. The risk for perinephric hematoma in theory is reduced because the kidney capsule is not compromised, although in reality capsular perforation does occur, with one case series demonstrating a pericapsular hematoma in >50% of high-risk patients. The benefit of a transjugular biopsy is that bleeding can be addressed at the time of the procedure. However, the procedure is not risk free, with the possibility of contrast nephropathy and the higher percentage of inadequate samples. One study demonstrated adequate samples in only 73% of transjugular biopsies compared to 97% in percutaneous biopsies. In addition, the expense associated with a transjugular biopsy is more than that of a standard percutaneous biopsy.

The open or laparoscopic surgical kidney biopsy is an alternative to either the percutaneous biopsy or transjugular biopsy. This surgical procedure allows procurement of multiple cores or a tissue wedge and gives the ability to directly visualize and control any bleeding that develops. The surgical biopsy results in extended recovery time and anesthesia-related and surgical risks associated with a surgical procedure. As a result, surgical biopsies are rarely performed. They are sometime reserved for patients who are undergoing a partial nephrectomy for tumor removal who also have a concern for underlying kidney disease. However, in so doing, the core obtained must be far away enough from the renal mass so as not to exaggerate fibrosis as it pertains to regions of the kidney remote from the mass.

Additional Readings

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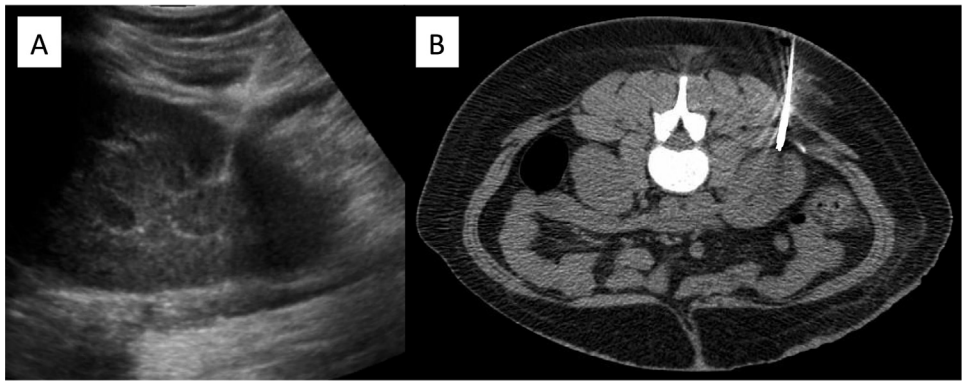

Figure 1. Biopsy needle insertion. (A) Ultrasound shows needle abutting kidney capsule with core track within kidney parenchyma. (B) Computed tomographic image shows trochar inserted and abutting kidney.

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The Biopsy Core

The number of core samples required for diagnosis is variable and depends on the diagnostic concern and is therefore an important reason for the biopsy to be performed by a nephrologist familiar with the clinical concern. In standard preparation, enough sample must be present to divide into fixative for light, immunofluorescence, and electron microscopy. Usually 2 cores are sufficient and can be divided into the appropriate fixatives. Core samples obtained from random sites of autopsied kidneys have demonstrated no variability in pathology based on multiple biopsy location. Therefore, cores obtained from the same general area will not be biased by sampling error.

Ideally, biopsy cores should contain predominantly cortical tissue because this is the location of glomeruli. Medullary samples will generally be void of glomeruli and thus preclude making a diagnosis if there is glomerular involvement. It is suggested that the cores be divided in a manner to maximize glomeruli in each of the respective samples. Needle size will influence the number of glomeruli obtained. The diameter of a 14-gauge needle is 1,000 μm; a 16-gauge needle, 700 μm; and an 18-gauge needle, 350 μm. With the average diameter of an adult glomerulus being 250 μm, an 18-gauge needle will lead to inadequate samples and fragmented glomeruli. When comparing a 14-gauge and 16-gauge needle, the majority of studies show a slight increased risk for hematoma formation with the former with no difference in glomeruli between the 2 sizes. Therefore, a 16-gauge needle will result in an adequate sample with minimal bleeding complications. Although the number of glomeruli required to make a diagnosis by light microscopy is variable, estimates of 15 to 20 glomeruli are suggested to adequately claim a sufficient sample. This can usually be achieved with 1.5- to 2-cm-long cores of tissue. Fewer glomeruli can still provide a diagnosis but with less certainty. Figure 2 demonstrates a method for dividing 2 cores obtained from a kidney biopsy. After cores are obtained, the operator should examine the cores with a dissecting scope or magnifying glass to determine whether the sample has glomeruli present. If there are no adequate glomeruli identified, additional samples may be required. It is recommended not to exceed 5 passes to obtain tissue because bleeding risk may increase at this level.

Samples for light microscopy should be placed into a 10% buffered-aqueous formaldehyde, or formalin,

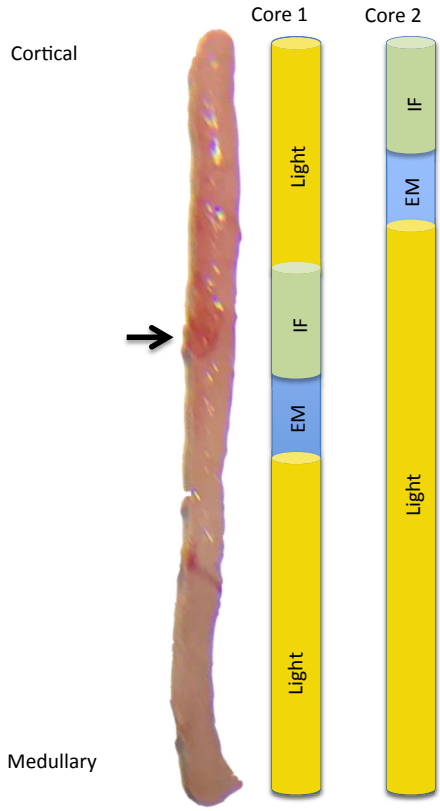

Figure 2. Kidney biopsy core, with cortical and medullary sides indicated. Arrow points to a vascular tuft, most consistent with a confluence of glomeruli. The core should be divided into samples for light, immunofluorescence (IF), and electron microscopy (EM). Samples should be divided in a way to ensure cortical tissue in each solution to maximize the presence of glomeruli.

solution. This solution allows for rapid fixation and is an excellent transport medium that is stable at room temperature. Formalin-fixed paraffin-embedded samples can also be used for immunohistochemistry studies or, if need be, for electron microscopy studies. Hematoxylin-eosin (H&E) staining is the most common stain used in pathology, including renal pathology. Hematoxylin is a dark blue or purple stain that is basic and binds acidic substances such as DNA or RNA, thereby staining nuclei blue or purple (Fig 3A). Eosin is a pink stain that is acidic and binds positively charged substances such as cytoplasmic protein. Eosin will stain cytoplasm in a reddish-pink color and collagen in a paler pink color. H&E stain is most useful for evaluating the integrity and cellularity of a glomerulus and can provide information on renal tubule epithelial integrity, mesangial cellularity and sclerosis, and degree of interstitial infiltrate. The hematoxylin phloxine saffron stain is an excellent stain to identify fibrinoid necrosis in vessels and capillaries and is a better stain to quantify collagen in areas of fibrosis (Fig 3B).

Periodic acid–Schiff stain is used to identify polysaccharides. The reaction involves oxidation of hydroxyl groups (vicinal diols) in glycogen, glycoproteins, and

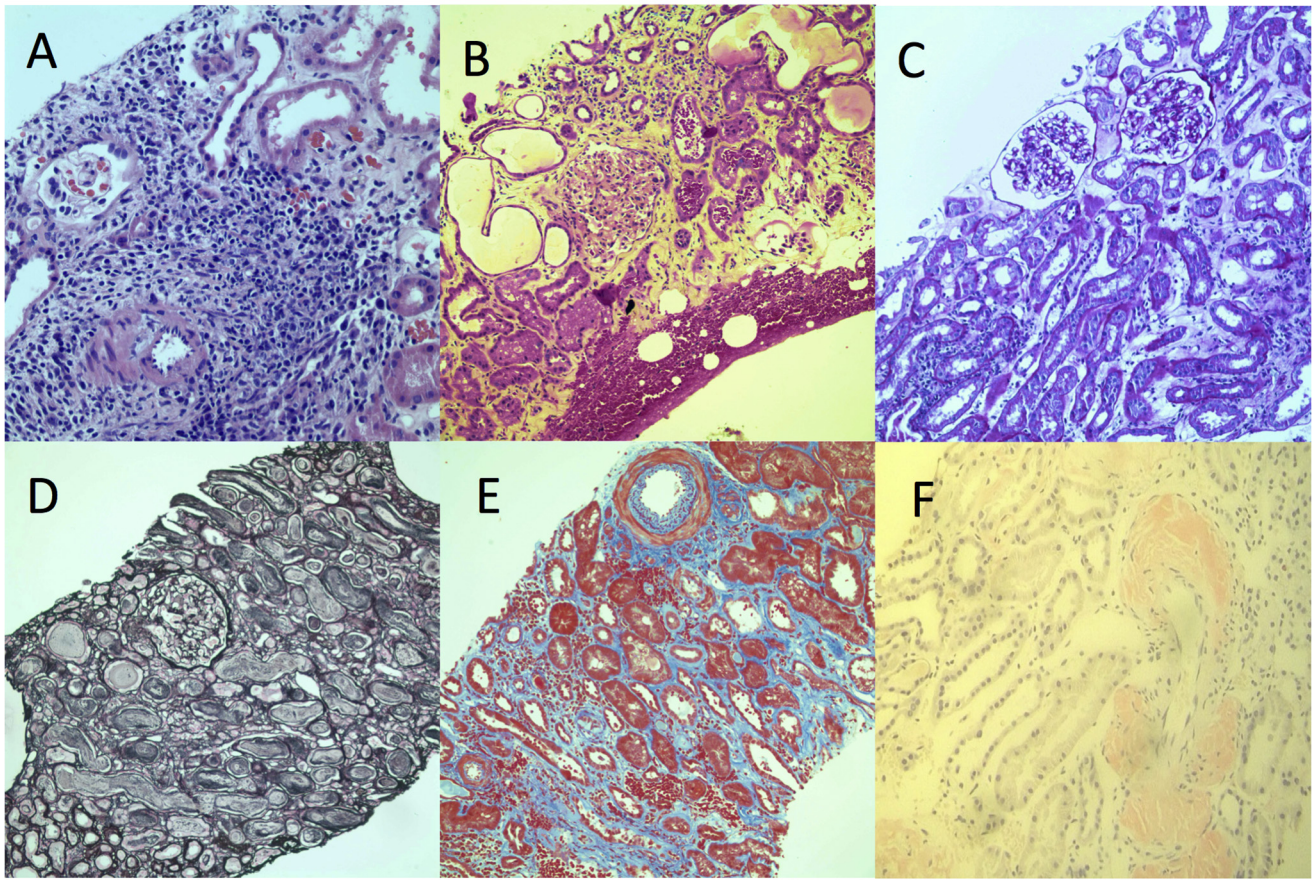

Figure 3. Light microscopy of kidney biopsy samples. (A) Hematoxylin-eosin stain (original magnification, ×100). Nuclei will stain deep purple and cytoplasm pink. (B) Hematoxylin phloxine saffron stain (original magnification, ×100). Areas of fibrous tissue will stain yellow-orange. (C) Periodic acid–Schiff stain (original magnification, ×100). Polysaccharides in basement membranes will stain deep purple. (D) Jones stain (original magnification, ×100). (E) Trichrome stain (original magnification, ×40). This stains cytoplasm as red and collagen as blue. (F) Congo red stain (original magnification, ×200). Amyloid fibrils are stained red in the vessel and interstitium.

glycolipids, resulting in a purple staining pattern (Fig 3C). Because these carbohydrates are more commonly found in basement membranes, periodic acid–Schiff stain is useful to judge increased thickness of tubular and glomerular basement membranes in biopsy specimens from patients with diabetic nephropathy. Jones stain is a methenamine silver stain with an H&E counterstain that is also used to assess basement membranes (Fig 3D). Areas of the glomerular basement membrane that show spikes and holes on Jones-stained sections are suggestive of membranous glomerulopathy.

Trichrome stain uses 2 or more dyes that are used to selectively differentiate basic tissue components. The use of multiple dyes allows for cytoplasm to be visualized as red and collagen as blue. In kidney tissue, the presence of blue staining areas on trichrome-stained sections will indicate the presence of collagen in areas of fibrosis (Fig 3E). In addition, immune complexes may appear as red granules with trichrome stain. Other staining protocols may be used based on the underlying concern. One stain that is used with frequency in patients when there is suspicion for amyloidosis is Congo red. Congo red is used to stain amyloid deposits, giving it a reddish hue on light microscopy and an apple-green birefringence under polarized light (Fig 3F).

Immunohistochemistry or immunoperoxidase stains can be used on formalin-fixed tissue sections. Immunohistochemistry involves immunohistochemical staining for many common antigens and can be correlated with findings on H&E-stained sections because the samples are obtained from the same block. One significant drawback to immunohistochemistry is that there can be a high degree of background staining that can make interpretation difficult (Fig 4A).

Samples for immunofluorescence studies are fixed in Michel tissue fixative. The antigens that are routinely examined include IgG, IgM, IgA, complement components C3 and C1q, fibrinogen, and κ and λ light chains. There is a high signal to noise ratio with immunofluorescence allowing for excellent detection of antigen in the interstitium, tubular membranes, and glomerulus. In addition, staining patterns in the glomerulus can separate mesangial from capillary basement membrane staining (Fig 4B).

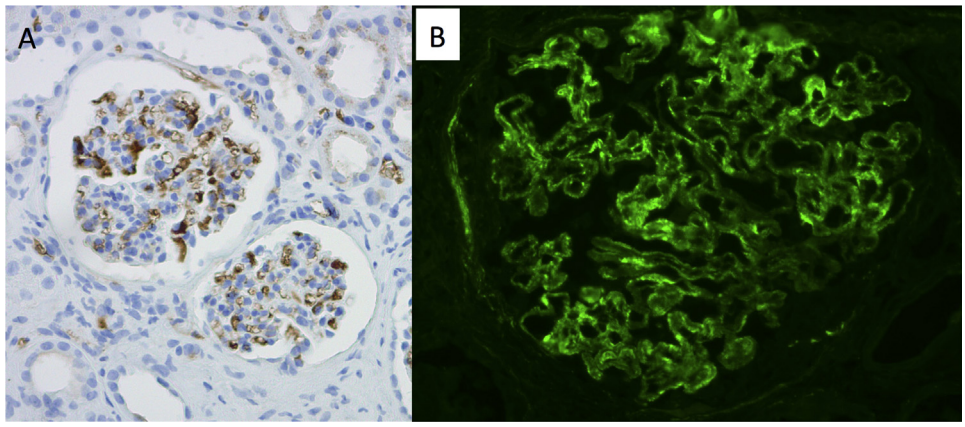

Figure 4. Immunohistochemistry (IHC) and immunofluorescence microscopy of kidney biopsy specimens. (A) Detection of immunoglobulin A using IHC; immune complexes appear as brownish material in the mesangium. (B) Detection of C3 using immunofluorescence (original magnification, ×400).

Tissue samples for electron microscopy are fixed in a glutaraldehyde solution. Initial thick sections are stained with toluidine blue. One to 2 glomeruli are usually selected for ultrastructural studies using a transmission electron microscope. The ultrastructural examination shows glomerular capillary loops, mesangium, and parietal cells at Bowman's capsule (Fig 5). If glomeruli are absent in the glutaraldehyde sample, glomeruli can be prepared from paraffin-embedded tissue. If the biopsy is technically difficult or with high risk and only 1 core can be obtained, respective tissue samples are often placed in formalin and Michel solution only, knowing that adequate electron microscopy interpretation can be obtained from a formalin-fixed sample. This will minimize sample collection and adverse complications in a high-risk biopsy patient.

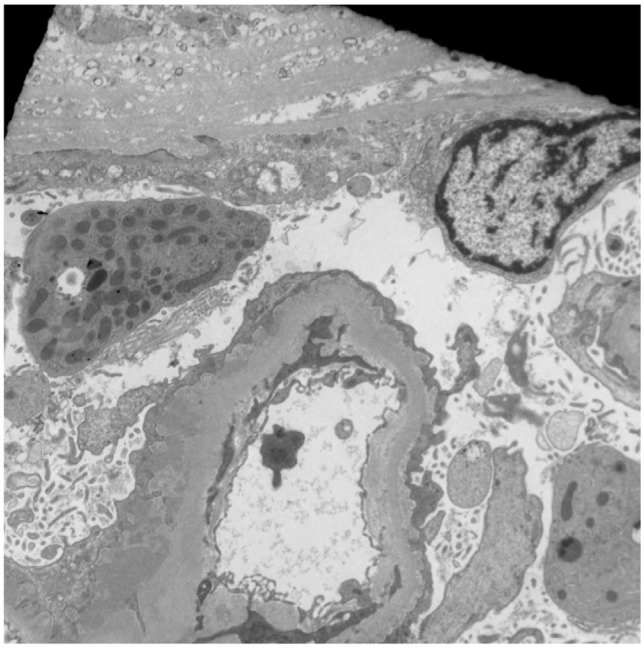

Figure 5. Electron microscopy of a capillary loop (original magnification, ×4,000). Dense deposits in the basement membrane appear as darkened areas within the membrane.

Table 3. Complications Associated With Kidney Biopsy

Complication	Comment
Bleeding	Most common complication
Hematoma (75%)	Develop in a high percentage of patients; visualize active extravasation at biopsy site with ultrasonography
Subcapsular bleed (<1%)	Significant bleeding may lead to subcapsular accumulation and resistant HTN (Page kidney)
Retroperitoneal bleed (5%-10%)	Complication of persistent bleeding or disruption of clot over biopsy site; image with CT or ultrasonography and follow up
Microscopic (>90%) or gross (40%-50%) hematuria	Persistence may lead to clot formation in kidney or bladder resulting in obstruction and hydronephrosis
Lumbar vessel laceration (<1%)	Requires a selective angiogram to identify the bleeding vessel
AVF formation (<5%)	Benign and can be followed up; should be intervened upon if it results in persistent bleeding, resistant HTN, high-output HF, or AKI
Pain (30%-50%)	May radiate into inguinal region or periumbilical region; will usually subside and should be treated with acetaminophen; if persistent, should result in re-imaging the kidney
Infection (<5%)	Low risk, but risk is worsened with skin infection, pyelonephritis, bleeding, or poor sterile technique
Nephrectomy (<1%)	Incidence is very low and with IR procedures, not common
Death (<1%)	Incidence is very low and is worsened by bleeding risk

Abbreviations: AKI, acute kidney injury; AVF, arteriovenous fistula; CT, computed topography; HF, heart failure; HTN, hypertension; IR, interventional radiology.

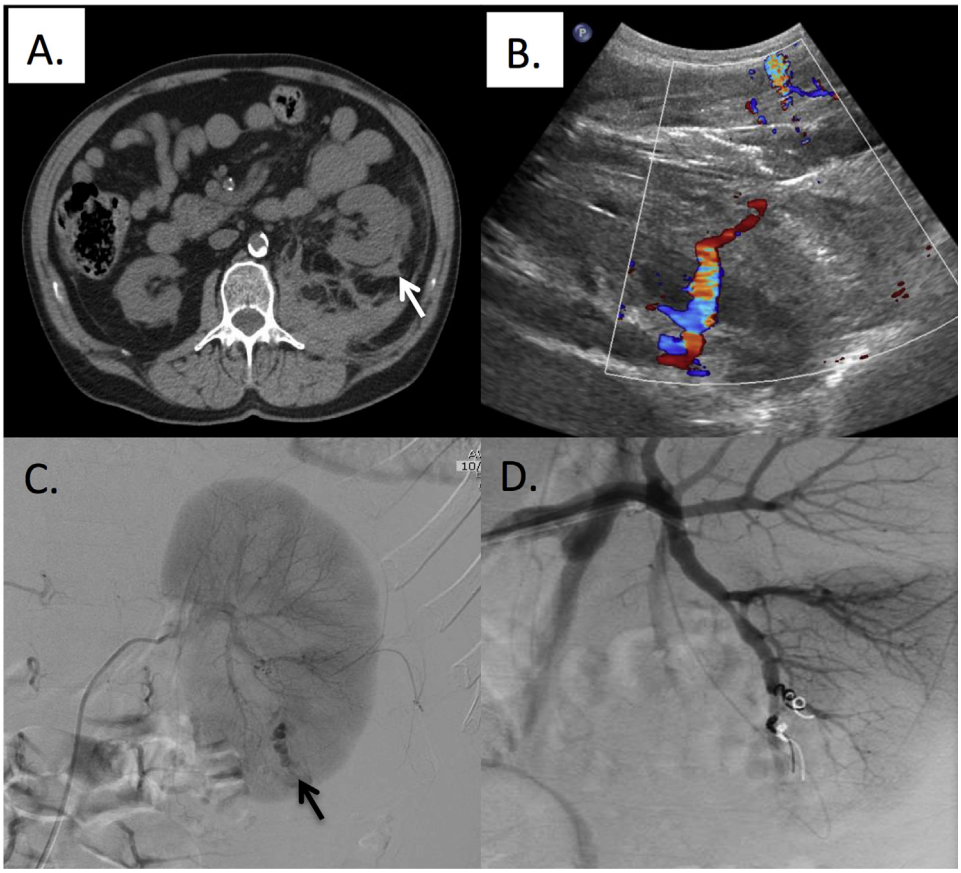

Figure 6. Bleeding as a complication of kidney biopsy. (A) Computed tomographic image with arrow pointing to a hematoma with resulting retroperitoneal hemorrhage. (B) Doppler ultrasound shows active extravasation of blood after biopsy. (C) Fluoroscopy shows active extravasation of contrast from a site of persistent bleeding. (D) Coiling of a vessel that was actively bleeding in panel C.

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Complications

Case 4: *A 56-year-old man with a history of new-onset proteinuria has just undergone a kidney biopsy. The biopsy was technically difficult due to the patient's obesity. Despite this, 2 cores were obtained after 6 passes with a 14-gauge needle. Immediately after the procedure, a hematoma was visualized and pressure was applied. In the recovery area, the patient has difficult-to-control blood pressure with increasing values, currently at 172/113 mm Hg.*

Question 4: Based on this presentation, what is the best next step in the management of this patient?

a) Obtain a repeat ultrasound
b) Provide the patient with oxycodone
c) Administer hydralazine, 10 mg, intravenous push once
d) Start the patient on amlodipine, 10 mg, and have him follow up in 1 week

For the answer to the question, see the following text.

There are both minor and major complications that can occur following a percutaneous kidney biopsy that lead to poor outcomes (Table 3). Bleeding events are the most common, which is likely explained by the great vascularity of the kidneys, which receive 25% of the cardiac output. In addition, the location of the kidneys deep in the retroperitoneum make it difficult to apply compression to halt bleeding. The relatively large needle size (14-16 gauge) used is also larger than core biopsy needles used to biopsy other organs. Finally, the consequences of kidney failure, including uremia and hypertension, increase the risk for bleeding.

The most common bleeding complication is the retroperitoneal hematoma (Fig 6A). Hematomas may be visible immediately postprocedure in >75% of patients undergoing a biopsy. However, a symptomatic hematoma that leads to transfusion is seen in only 5% to 10% of

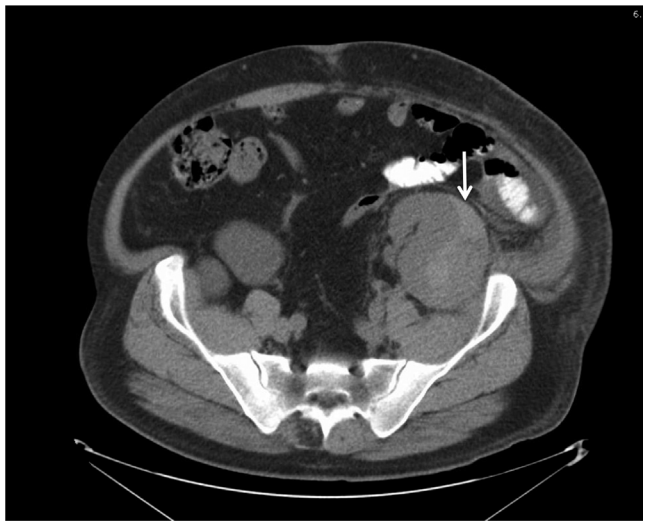

Figure 7. Accumulation of subcapsular blood causing compression of the kidney. White arrow points to capsule with blood underneath.

patients. Active extravasation of blood into the hematoma can often be visualized using duplex Doppler ultrasound after the biopsy. In most cases, bleeding is stopped with 5 to 10 minutes or less of direct pressure to the site of the biopsy (Fig 6B). If bleeding persists and the hematoma continues to increase in size, it may be necessary to embolize the bleeding vessel (Fig 6C and D). This is a rare occurrence in <0.5% of patients. Continued bleeding into the subcapsular space can potentially lead to compression of the kidney; however, this also is a rare complication (Fig 7).

Another important bleeding complication is gross hematuria. In rare instances, this may lead to clot formation and urinary outlet obstruction with AKI. This can usually be managed conservatively with Foley catheter insertion and bladder irrigation if needed (Fig 8).

Predictors of bleeding vary based on multiple studies. Risk for bleeding tends to be worse in younger patients, females, and patients with prolonged partial thromboplastin times. In addition, bleeding has been shown to be worse in patients with elevated systolic and diastolic blood pressures. Optimization of blood pressure and attention to risks may help reduce the risk for a bleed in patients. Bleeding can also be minimized by the use of injectable gel foam at the time of biopsy, a technique often used by interventional radiologists.

An arteriovenous fistula occurs after 0.5% to 10% of biopsies, but they are usually asymptomatic. In rare cases, arteriovenous fistulas cause hematuria, high-output heart failure, resistant hypertension, or AKI. Doppler ultrasonography can be used to confirm their presence. Most resolve spontaneously over a period of months, although an enlarging or symptomatic arteriovenous fistula can be corrected using arterial embolization.

Nephrectomy resulting from a kidney biopsy is rare, with a reported frequency < 0.5%. The risk for death from a biopsy is believed to be <0.1% in most clinical practices.

The patient in case 4 most likely has Page kidney and the kidney should be evaluated using repeat ultrasonography or CT. Treatment is largely supportive, but the patient should be admitted and blood pressure should be controlled immediately to prevent worsening extravasation of blood. Because the hypertension is renin mediated in Page kidney, an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker should be used. Thus, the best answer is (a).

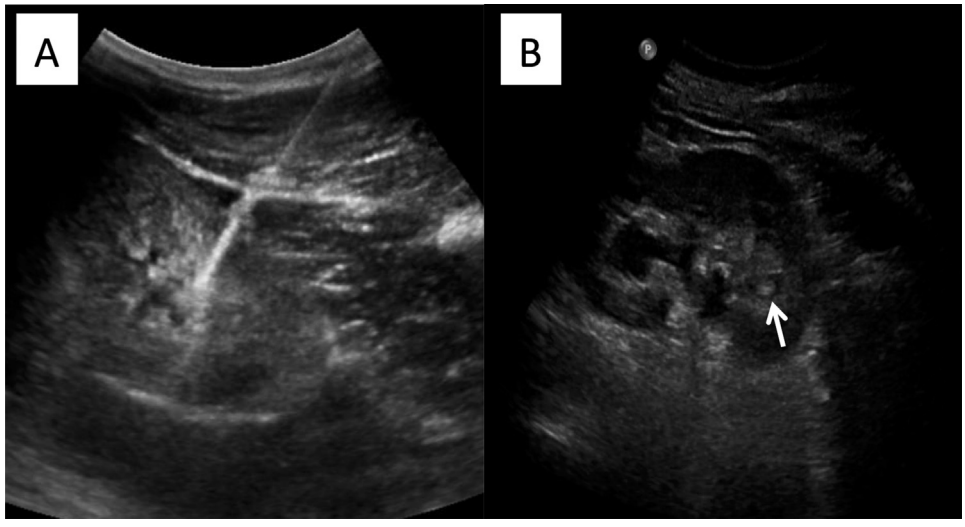

Figure 8. Urinary outlet obstruction caused by bleeding after kidney biopsy. (A) Ultrasound image of a biopsy shows core being obtained in left lower pole. (B) Image 5 days after biopsy when patient reported inability to void. Ultrasound demonstrates hydronephrosis and clot (white arrow) within kidney.

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Future Directions

Current nephrology practice uses percutaneous kidney biopsy to diagnose kidney disease with the hopes of providing therapeutic and prognostic information that can alter disease progression. Precision medicine as it pertains to nephrology can expand the role of the kidney biopsy and provide a patient with a personalized disease profile and possibly a targeted therapy. Precision medicine relies on the integration of techniques, including genomics and proteomics, to extract molecular diagnostic information from kidney tissue, blood, and urine samples and allowing for the identification of disease-specific biomarkers. Currently ongoing clinical trials are in various phases to collect kidney biopsy specimens for the study of causes of AKI, chronic kidney disease, and glomerular disease. The information gained from these studies over subsequent decades may allow nephrologists to take a targeted approach toward the treatment of these heterogeneous disease states.

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