Kidney Biopsy

4

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The percutaneous renal biopsy (PRB) is a little over 60 years old, and despite the advances in other diagnostic tests, it remains critical to the diagnosis, management and prognosis of the renal transplant and many nephrological conditions [1].

In experienced hands using real-time ultrasound and spring-loaded biopsy guns, the procedure has become routine, often performed as a day case, and should have a diagnostic yield of 95 % with a significant complication rate of <5 % [2]. This chapter will discuss the indications and practical aspects of nondirected renal biopsy.

Indications and Contraindications for Renal Biopsy

However prosaic biopsies have become, obtaining a suitable diagnostic core safely is a skilled procedure; thus, for those providing a renal biopsy service and those requesting a biopsy, the risk:benefit ratio for the patient remains an important consideration. If the operators are relatively inexperienced and doing infrequent biopsies, then the risk for the patient is likely to be significantly higher.

Indications (See Table 4.1)

This will very much be determined by individual circumstances; whether the likely diagnosis can be established without a biopsy, how high risk the treatment for the presumed diagnosis is and how safely a biopsy could be done. In essence, what is the question being asked in terms of diagnosis, prognosis, response to treatment, and can it be reliably answered without a biopsy? A unit with a fairly inexperienced biopsy service should have a higher threshold for PRB and may benefit from developing skilled urine microscopy.

Acute Kidney Injury: In the majority of cases of AKI, the diagnosis is not in doubt and the acute tubular injury is explained by preceding hypotension, sepsis or medication especially in the setting of pre-existing CKD; in these circumstances a biopsy is likely to contribute little but hazard. However, there are times when a biopsy can add substantially to the management of AKI (see Table 4.1):

1. Rapidly progressive glomerular nephritis AKI. In the setting of an active urine deposit, a biopsy may be critical to exclude a rapidly progressive glomerular nephritis for which getting the *correct* treatment urgently has very significant consequences (e.g. anti-GBM disease or infective endocarditis).
2. A proportion of patients will present with AKI in the absence of any obvious hypotension or sufficient comorbidity to fit with the degree of renal impairment, and in these individuals a biopsy may diagnose either a chronic underlying renal disease or an active unanticipated renal disease such as acute interstitial nephritis.
3. Occasionally AKI occurs in the setting of unexplained constitutional illness, and assuming there is convincing evidence of direct renal involvement (haematuria, proteinuria or pyuria), then a renal biopsy may be the most direct approach to a diagnosis (e.g. sarcoid, tuberculosis, systemic vasculitis, cryoglobulinaemia, endocarditis).
4. Finally, in a patient who would be expected to recover renal function within days or a few weeks of a limited renal insult. When this is not the case and the persistence of

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Table 4.1 Indications for nondirected renal biopsy

AKI	1. Rapidly progressive AKI
	2. AKI without obvious explanation
	3. AKI in the setting of undiagnosed systemic illness
	4. Failure to recover from AKI
Proteinuria	Nephrotic syndrome in adults
	Steroid-resistant nephrotic syndrome in children
	Moderate unexplained proteinuria with renal impairment or haematuria
Microscopic haematuria	Non-lower urinary tract haematuria with renal impairment, hypertension or in potential live donor
Pyuria	Unexplained pyuria in the context of renal impairment
Tubular dysfunction	Unexplained tubular abnormalities without an obvious aetiology
CKD	Unexplained CKD in the setting of relatively preserved renal size/cortex
Diagnosis and monitoring of systemic disease	Response to treatment and prognosis in, e.g. vasculitis, SLE, myeloma, sarcoid
Transplantation	Graft dysfunction (exclusion of rejection, recurrent disease, BKV and other infections, quantification of IFTA)
	Protocol biopsy

oliguria is unexpected, then a biopsy may be helpful in determining prognosis of recovery or establishing renal disease such as acute TIN or renal infection. As a rule of thumb if the patient is still oliguric 6 weeks post-AKI then a biopsy may be helpful; however, the timing for this would be sooner if the primary insult was mild or the threshold would be higher if there have been multiple significant insults.

Nephrotic syndrome is a common indication for renal biopsy; however, in paediatric practice, it is unusual to biopsy a patient at first presentation as the real issue is whether the nephrotic syndrome is steroid responsive. Thus, patients are only offered a biopsy if they fail to respond to a course of steroids. In adults the equation is very different; for example, a significant proportion of nephrotic adults will have membranous glomerulonephritis, amyloid or mesangiocapillary glomerulonephritis for which there is no evidence that steroid monotherapy has any benefit. Committing all nephrotic adults to a prolonged course of steroids on spec would inflict serious side effects with no benefit for a significant proportion, and thus most units have a low threshold for biopsy in adults with nephrotic syndrome.

In patients with isolated sub-nephrotic range proteinuria, the indications are more controversial; significant proteinuria in any renal disease is an adverse prognostic factor, and reduction of proteinuria by any means such as control of blood pressure and blockade of the renin angiotensin system improves the prognosis. Therefore, the majority of patients are going to receive this treatment whatever the underlying condition; however, it is common to biopsy nondiabetic patients with isolated proteinuria >1 g/day or a consistent PCR >100 to exclude other potentially treatable conditions particularly if there is evidence of declining renal function.

With *isolated microscopic haematuria*, it is usual, in patients over 40, to exclude lower urinary tract disease/malignancy before assuming a renal lesion. The underlying renal pathology is usually either IgA glomerulonephritis, hereditary abnormalities of the GBM (e.g. Alport syndrome) or thin basement membrane disease. In this setting there is very little in the way of specific treatments and thus benefits of a biopsy predominantly relate to prognosis for the patient (particularly for insurance purposes), especially in the context of potential live donation, and family if excluding a heritable GBM abnormality. In practical terms and in the absence of the indications above, most units will merely recommend observation unless hypertension or renal impairment intervenes.

It is conventional wisdom to avoid a renal biopsy in the context of a UTI for fear of generating an abscess; however, it is not unheard of to make a diagnosis of pyelonephritis on a biopsy with a culture-negative MSU, and there is little or no data indicating the degree of risk for abscess formation following a biopsy. Similarly, the diagnosis of renal TB or sarcoid may only be made following a biopsy in a patient with sterile pyuria and renal impairment.

It is rare that a biopsy is necessary for the diagnosis of tubular disorders, but very occasionally electron microscopy can reveal the underlying cause, for example, in Fanconi syndrome an underlying mitochondrial cytopathy, dysproteinuria and heavy metal poisoning are worth considering if the primary diagnosis is not obvious.

Patients with CKD 4–5 with small kidneys are at very high risk from a biopsy, and it is much less common that the risk:benefit ratio justifies the investigation.

There is a stronger imperative if the primary disease cannot be diagnosed by less invasive tests, and there is a high likelihood of clinically relevant recurrence post-transplant. In practice this is rare; diseases with significant impact if not identified such as Goodpasture's syndrome, atypical HUS, systemic vasculitis and SLE can usually be diagnosed without recourse to a biopsy, and conditions such as IgA which require a biopsy for diagnosis have limited impact post-transplant and would not alter management. However, very rarely conditions with significant impact on a future transplant such as membranoproliferative GN and primary hyperoxalosis may only be diagnosed via renal biopsy.

Finally, renal biopsy can be critical in establishing a more systemic disease, and occasionally repeat biopsy can act as a barometer of disease control in the absence of other less invasive markers. Most commonly this is in the context of connective tissue diseases such as vasculitis and SLE with an active urine deposit. However, a biopsy may demonstrate deposition of light chains in myeloma or evidence of HIV-related nephropathy which might provoke treatment for either condition. Similarly biopsy of enlarged kidneys with dysfunction can diagnose infiltration and escalation of treatment in lymphoproliferative disorders.

Table 4.2 Contraindications to nontargeted native renal biopsy

Renal mass	Risk of neoplastic spread
Polycystic kidneys	High-risk and low diagnostic yield
Small end-stage kidneys	Very-high-risk and low diagnostic yield
Acute bacterial pyelonephritis	Risk of perinephric abscess formation, lower UTI is a relative contraindication
Solitary kidney, horseshoe kidney	Increased risk of dialysis dependence but relatively safe in experienced hands, open or laparoscopic biopsy alternatives
Obstructed kidneys	Increased risk of urinary leak
Bleeding diathesis	Absolute contraindication if uncontrolled, relative if correctable (see coagulation in renal disease chapter 52)
Uraemia	Relative contra-indication, due to platelet dysfunction; where possible correct prior to biopsy
Severe hypertension	Kidney vasculature poorly able to autoregulate even if blood pressure is acutely controlled
Severe obesity	Biopsy becomes technically more difficult and dangerous with increasing obesity. Transjugular, laparoscopic and open biopsy may offer significant advantage
Uncooperative patient	Absolute contraindication if unable or unwilling to cooperate with breath holding. If lacking capacity and biopsy essential, consider biopsy under a general anaesthetic
Third trimester pregnancy	Relatively contraindicated, dilated system, sitting, risk of foetal loss, but very rarely necessary after second trimester and before delivery
Vascular abnormalities	Aneurysms (e.g. PAN), arteriovenous malformations

Contraindications

In the majority of patients with contraindications to renal biopsy, it is possible to make a diagnosis and management plan based on urine microscopy and other clinical features. However, it is important to note that most of the contraindications to renal biopsy (Table 4.2) are relative in that if a biopsy is *really* critical to patient management, it is often possible to reduce the risk of a PRB or to use alternative approaches. The coagulopathy of renal failure is covered in chapter 52, but a uraemic patient is likely to have significant platelet dysfunction and in practical terms there is no routinely available test that can predict this accurately (including bleeding time). In uraemic patients there is a correlation with risk of bleeding at haemoglobins below 10 g/dl; thus, in high-risk patients it is common to optimise the risk by dialysis (if dialysis dependent) and transfusion the day before a biopsy. Amyloidosis was said to increase the risk of PRB, but a recent retrospective study has demonstrated no apparent excess in complications.

It is important for the unit to have a robust system in place to ensure that low molecular weight heparins (which will not be detectable with PT and PTT assays) are crossed off 24 h prior to biopsy.

Finally, an increasing proportion of renal patients are on anti-platelet agents. Conventionally aspirin is stopped a week before an elective biopsy; however, when given for secondary prevention, there seems to be an increased risk of acute coronary events [3] and cerebrovascular events [4] on stopping aspirin. A recent review suggests stopping clopidogrel 3–5 days prior to surgical procedures and continuing aspirin in general patients [5]. Clearly the risk:benefit ratio needs to be decided on an individual basis with the caveat that a patient with significant cardiovascular morbidity is unlikely to tolerate a substantial bleed well.

Desmopressin (DDAVP) V2 antagonist results in a release of stored ultra-large von Willebrand factor multimers and factor VIII. The effect lasts from 1 to 24 h and can be used in uraemic high-risk patients to promote platelet aggregation. One randomised trial demonstrated a reduction in bleeding and haematoma size with prophylactic DDAVP in PRB [6]. However, it can induce coronary vasospasm in patients with ischaemic heart disease, and our practice is to ensure that it is given slowly (>1 h).

Procedure PRB

Renal biopsies are now generally obtained using spring-loaded biopsy guns using 14–18 gauge needles (typically 16G for native and 18G for transplants); increasingly the guns are also disposable, but if using a non-disposable gun, a robust process for post-procedure sterilisation is mandatory. Biopsies should be performed under real-time ultrasound (curvilinear ultrasound probes are preferred as lower-frequency range gives a larger field of view and greater depth than linear probes). The probe should be covered by a sterile, disposable probe cover procedure performed with full aseptic technique.

The technique for native biopsies is beautifully illustrated in the video produced by Dr Peter Topham and Dr Sue Carr at Leicester Royal Infirmary (see Video 4.1). The technique for transplant biopsies is slightly different and again nicely illustrated on the video produced by Mr Peter Veitch and Arundhati M. UCL Centre for Nephrology (see Video 4.2).

Skewing things in your favour by ensuring a good- and high-resolution US scanner, properly darkened room and good positioning of a relaxed patient is fundamental to success.

It is important to note that patients are often, understandably, nervous about the procedure, and it is also very important to ensure that the patient is thoughtfully talked through the procedure and reassured.

It is rarely necessary to biopsy a patient in the third trimester, but sometimes a biopsy is required in the second trimester, and if not possible to do this prone, the patient can be sat upright on the bed with arms and head resting on a table. Obese patients can sometimes be biopsied lying laterally with pillows supporting their middle.

Anatomy and Complications and Consent

See Figs. 4.1, 4.2, 4.3 and 4.4.

Complication rates in the literature vary significantly depending on definition, how studiously they were looked for and how high risk the biopsy. There is almost certainly a significant publication bias in favour of low rates. What follows is a rough and hopefully reasonable summation of the risks; ultimately complications will depend on local practice and experience, but individuals and units should be audited against these outcomes on a regular basis [7–9].

Temporary local pain and discomfort on administration of local anaesthetic is universal but should subside rapidly and patients should be prewarned of this. Native renal biopsies tend to be more uncomfortable than biopsy of a superficial denervated renal transplant kidney.

1. Failure of technique or diagnostic inadequacy of 5 %.
2. Percutaneous infection with aseptic technique seems extremely rare and the risk of a renal/perirenal abscess following a biopsy in the presence of urosepsis is difficult to define and neither tends to be consented for.
3. Biopsy of non-renal tissue should be rare; however, it is not unheard of to obtain small bowel with native PRB; anecdotal evidence seems to suggest this is of little consequence. Biopsy of large bowel or pancreas is rarer but potentially more serious, and patients should be carefully reassessed if this occurs.
4. Macroscopic haematuria (1–2 %).
5. Arteriovenous fistulae (AVF) on the other hand appear to be very common with an incidence of roughly 10 % on screening. As 95 % of AVF appear to resolve

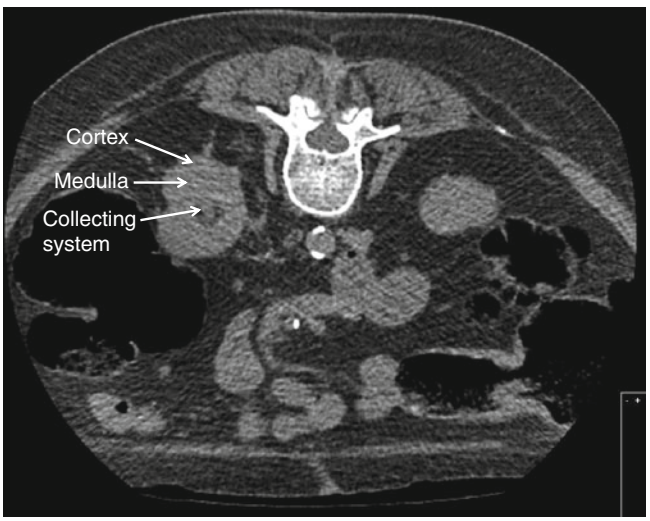

Fig. 4.1 Prone unenhanced CT at the level of the lower pole of the left kidney

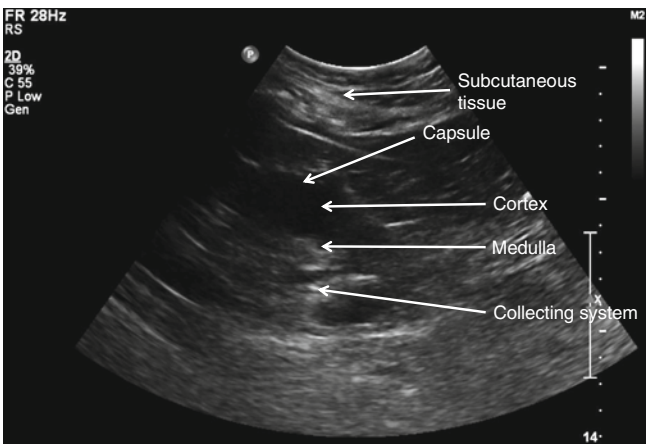

Fig. 4.2 Prone ultrasound, same patient

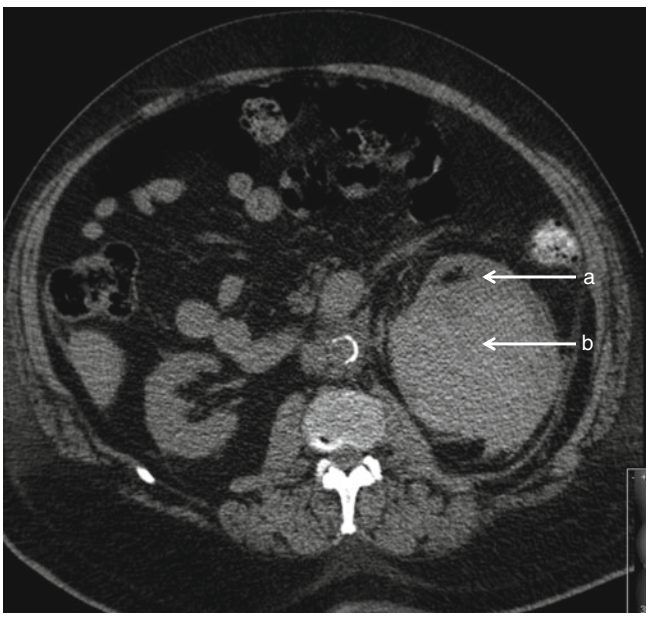

Fig. 4.3 CT scan of subcapsular haematoma following biopsy of the left kidney. The left kidney (*a*) is displaced anteriorly, secondary to a high-density collection (*b*)

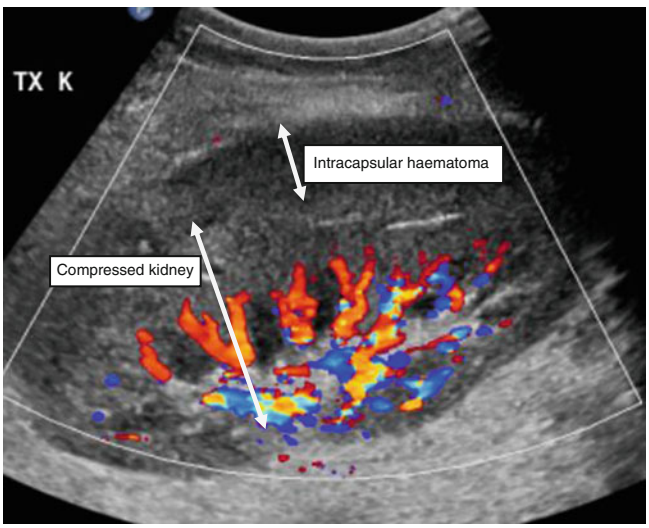

Fig. 4.4 Intracapsular haematoma causing gross compression of the kidney (Page kidney) and anuria in a transplant recipient. Urine flow was restored instantly with surgical decompression

spontaneously, this complication tends not to be quoted for consent. However, AVF that do not resolve pose a potential hazard for future biopsies (a bruit over the kidney and fall in GFR should raise suspicion) or significant steal from the kidney.

6. Perirenal haematoma appears to be a very common complication with rates of 57–85 %, although this data comes from studies done 30 years ago, and for the majority of patients, haematoma in itself appears to have had little consequence. However, rarely a subcapsular haematoma may cause a 'Page kidney' (see Figs. 4.3 and 4.4) and, in a single kidney, acute oliguria requiring urgent surgical decompression.
7. Bleeding requiring transfusion, 1 % if standard risk and >2 % if high risk.
8. Embolisation rate post-PRB is rather dependent on access to this, but we quote rates of 1:400.
9. The data on loss of kidney or nephrectomy is scant but usually quoted at less than 1 in 1,000 and is important to discuss for transplant and solitary kidney biopsy.
10. Mortality is associated with PRB and the literature suggests this to be 1 in 2,000–5,000 biopsies.

Acute oligoanuria post-transplant is likely due to the following:

(a) Shock: this is usually pretty obvious.
(b) Clot retention: easily diagnosed by US or catheterisation.
(c) Page kidney: this may cause complete anuria in a transplant, but often missed in native biopsies once identified urgent surgical decompression can instantly restore perfusion to a transplant kidney but risks further bleeding by removing any tamponade; the optimum option is to surgically decompress the kidney and perform selective radiological embolisation immediately if haemostasis cannot be achieved.
(d) Urinary leak: this may be identifiable on delayed film MAG-3.

Post-biopsy Monitoring

Typical post-biopsy monitoring would be pulse and blood pressure monitoring as follows: every 15 min for an hour, then if stable; every 30 min for 2 h, then if stable; every hour for 4 h, and then if stable and passed urine (without haematuria), mobilise and discharge; if an inpatient (high-risk patient), then continue four-hourly monitoring.

The most critical aspect of post-biopsy monitoring is that nursing and medical staff are familiar with the procedure and are comfortable escalating monitoring and requesting medical review at the first sign of a complication.

The timing of complications is important and somewhat controversial; one large study detected 42 % of complications within 4 h, 67 % by 8 h, 85 % by 12 h and 89 % by 24 h [6]. This data would imply that day case biopsies would not be safe, yet a third of complications occurring after 8 h does not seem to be general experience, and day case biopsies in standard-risk patients seem to have a high safety record.

Day Case vs Inpatient Procedure

In the last two decades, standard-risk PRBs have been increasingly performed as day case procedures. The published audits seem to have a good safety record, benefits to patients and significant cost savings [10, 11].

There are no standard guidelines for who is suitable for day case biopsy but the criteria below seem to have been arrived at independently by several units and represent a reasonable starting place.

Suggested criteria for day case renal biopsy:

1. Two kidneys ≥10 cm
2. Blood pressure ≤150/90
3. eGFR ≥30
4. Hb ≥10 g/dl
5. Platelets ≥100
6. INR ≤1.2 PTT ≤1.2
7. Off aspirin or clopidogrel for 7 days
8. Lack of significant cardiovascular co-morbidity
9. BMI ≤30 (not significant centripetal obesity)
10. A responsible adult to transport home and at home to provide care and support for 24 h post-transplant
11. Experienced operator and day ward staff

The good outcome data presumably, in part, reflects that patients suitable for a day case biopsy are carefully selected; thus, if the above criteria are breached, then the decision to proceed as a day case biopsy must be discussed with the patient and should be made at a senior level.

Example of day case and inpatient renal biopsy pro formas are attached and can be modified for local practice.

For inpatient biopsies it is less easy to be absolutist because there may be compelling reasons to perform a biopsy despite the increased risk, and depending on local expertise, options such as open, laparoscopic or transjugular biopsy might be employed.

Alternatives to PRB in High-Risk Patients (Table 4.3)

As levels of obesity and co-morbidity increase, we will be increasingly faced with high-risk patients. There are a variety of alternatives to stand PRB nicely summarised in a review by Stiles et al. [12].

Open Renal Biopsy (ORB)

The definitive series of ORB was of 934 patients and had 100 % tissue adequacy and apparently no significant complications [13]. Open (and laparoscopic) approaches

Table 4.3 Alternatives to PRB in high-risk patients

Technique	Advantages	Disadvantages	Possible indications
Open biopsy	Direct vision, very high diagnostic yield, direct haemostasis, suitable for ventilated patient	General anaesthetic, long recovery and hospitalisation, cost	Single kidney, kidney with multiple cysts, obese patient, patient unable to cooperate with breath holding
Laparoscopic biopsy	Direct vision, very high diagnostic yield, direct haemostasis, less invasive than open biopsy, suitable for ventilated patient	General anaesthetic, long recovery, hospitalisation, cost	Single kidney, kidney with multiple cysts, obese patient, patient unable to cooperate with breath holding
Transvenous biopsy	Suitable for grossly obese, contractures preventing PRB, abnormal clotting, diagnostic yield 78–97 % Suitable for ventilated patient	Contrast load, smaller sample size predominance of medulla	Simultaneous liver kidney biopsy, concomitant with dialysis line placement, obese patient, bleeding diathesis, patient unable to cooperate with breath holding

offer the distinct advantage of direct vision and direct haemostasis and thus can be helpful in patients with cysts or other focal abnormalities as well as other high-risk patients and those already ventilated. The need for general anaesthetic and significant recovery time however are not justified in standard-risk patients.

Laparoscopic Renal Biopsy (LRB)

There are several case series of LRB usually in the setting of high-risk patients. As with ORB direct vision means the diagnostic yield approaches 100 % and immediate haemostasis can be performed. This offers a significant advantage in patients with a body habitus preventing PRB, mild bleeding disorders or focal abnormalities of the kidney. As with ORB this technique obligates a general anaesthetic but is less invasive and the recovery time is likely to be less than for an ORB and again can be considered in patients already ventilated on ITU.

Transvenous Renal Biopsy (TVRB)

Transvenous renal biopsy (TVRB) (usually transjugular) has been reported in the setting of bleeding diathesis [14–17] or obesity [18] (mean BMI 44). The theoretical advantages are that (a) the capsule is less likely to be punctured, (b) any bleeding should be back into the vein, (c) any acute extracapsular bleeds demonstrated at the time can be embolised if significant and (d) tissue can be obtained in patients in whom the percutaneous approach is not feasible, e.g. grossly obese. Diagnostic yields of 78–97 % have been reported and, in the largest study to date, major complications of only 1 % [14], but other smaller studies have had significantly higher rates and it is easy to inadvertently perforate the capsule. In short TVRB is a useful technique for high-risk patients if there is sufficient local expertise; however, it is not without risk and remains extremely important to correct coagulopathies as much as possible prior to biopsy.

Standards for Renal Biopsy

In 2010 the British Association for Paediatric Nephrology published suggested standards for renal biopsy [2] which are also a useful benchmark for adult patients with some amendments to consider added in italics:

1. All patients should receive an appropriate patient information leaflet (PIL) about the biopsy procedure[1] (*in advance and, ideally, in their first language*) (*the patient or guardian should have a clear understanding of the indication for the biopsy*).
2. *Complication rates for macroscopic haematuria, transfusion, embolisation and loss of kidney (if single or transplant) should be quoted as part of consent.*
3. For both native and transplant biopsies, ≤3 passes should be achieved in 80 % of occasions.
4. There should be adequate tissue for diagnosis on 95 % of occasions.[2]
5. Major complications (defined as delay in discharge as a result in post-biopsy complications or requirements for further investigations or monitoring) should be <5 %.
6. *There should be on site access to interventional radiology and surgeons experienced in dealing with a major renal bleed.*

[1]The renal association has produced a PIL available on the website (www.renal.org), and there is a similar PIL available on MedlinePlus and includes Spanish translation.

[2]Adequacy: the general consensus is that for native renal biopsies, 10–15 glomeruli are an optimal number to exclude a focal glomerulonephritis (>20 ideal), but this definition of adequacy may be a little rigid as sometimes it is possible to make the diagnosis on a single glomerulus. Conversely, a sample of less than 10–15 may miss focal disease and therefore be unable to rule out other disease (such interstitial nephritis or rejection in transplantation). For transplant biopsies, the Banff classification requires >10 glomeruli and two arteries with a minimum of seven glomeruli and one artery. A more pragmatic definition of adequacy is that if the cause of the renal dysfunction is identified, then the sample was adequate, if not, then adequate only if containing ≥10–15 glomeruli.

7. *Operators should maintain a prospective audit of adequacy and complications.*

Informative, detailed request forms greatly assist the pathologist, uninformative ones do not; it is thus good practice to ensure that the indication and clinical details are of a high standard.

The workup of a renal biopsy is reviewed in more detail elsewhere [19]; however, assessment requires light microscopy always, immunohistochemistry frequently and electron microscopy occasionally. Although there are many different approaches to technical aspects of these, the most important factor is the competence of the pathologist who is giving a report on the specimen. Different pathologists have their own preferences for the number of sections, whether serial sections are cut, which stains are used, whether immunofluorescence usually on frozen sections or an enzyme method such as immunoperoxidase on paraffin sections is used for immunohistological studies and whether electron microscopy, if available, is necessary on a particular specimen. Importantly if your laboratory processes biopsies for immunoperoxidase, then it is often possible to retrospectively obtain tissue for electron microscopy (see Howie [20]). Renal pathology is a highly specialised field, and it is important to have close liaison between clinicians and pathologists as well as consider presenting difficult cases between renal teams and pathologists.

Finally pathology MDT meetings are an invaluable liaison between clinicians and pathologists, and it is important to document, in real time (ideally electronically), conclusions of these discussions and consequent treatment plans.

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