Chapter 9: Kidney Allograft Biopsy

9.1: We recommend kidney allograft biopsy when there is a persistent, unexplained increase in serum creatinine. (*1C)*

9.2: We suggest kidney allograft biopsy when serum creatinine has not returned to baseline after treatment of acute rejection. *(2D)*

9.3: We suggest kidney allograft biopsy every 7–10 days during delayed function. *(2C)*

9.4: We suggest kidney allograft biopsy if expected kidney function is not achieved within the first 1–2 months after transplantation. *(2D)*

9.5: We suggest kidney allograft biopsy when there is:
- **new onset of proteinuria *(2C);***
- **unexplained proteinuria ≥3.0 g/g creatinine or ≥3.0 g per 24 hours. *(2C)***

Background

Kidney allograft biopsies are performed for specific clinical indications, or as part of a surveillance program (or protocol). An 'indicated biopsy' is one that is prompted by a change in the patient's clinical condition and/or laboratory parameters. A 'protocol biopsy' is one obtained at predefined intervals after transplantation, regardless of kidney function. In both cases, the biopsy is obtained to find histological changes prompting treatment to improve outcomes. DGF is graft function low enough to require dialysis in the first week after kidney transplantation, or lack of improvement in pretransplant kidney function.

New-onset proteinuria (defined in Table 6) may indicate treatable causes of graft dysfunction, including acute rejection and thrombotic microangiopathy. In patients who already have proteinuria, an increase exceeding a threshold usually defined as 'nephrotic range' proteinuria, for example ≥3.0 g/g creatinine or ≥3.0 g/24 h, may indicate treatable causes of graft dysfunction.

Rationale

- Increased serum creatinine that is not explained by dehydration, urinary obstruction, high CNI levels or other apparent causes is most likely due to an intragraft parenchymal process, such as acute rejection, CAI, drug toxicity, recurrent or *de novo* kidney disease or BKV nephropathy.
- The optimal diagnosis and treatment of intragraft parenchymal causes of allograft dysfunction require an adequate biopsy.
- In patients with DGF, change in serum creatinine is not useful for ruling out acute rejection, and protocol biopsies are needed to rule out acute rejection.
- Proteinuria, or a substantial increase in proteinuria, may indicate a potentially treatable cause of graft dysfunction.

Biopsies for an increase in serum creatinine

Although serum creatinine has many limitations for estimating GFR (see Chapter 8), an unexplained rise in serum creatinine is generally indicative of a decline in GFR. Some fluctuation in creatinine can result from normal laboratory or physiological variability. Hence, only a persistent increase that is outside this normal, but poorly defined, range is clinically relevant. A 25–50% increase over baseline is often arbitrarily used in studies. At least one study suggested that a persistent 30% rise in serum creatinine was an excellent predictor of subsequent graft failure (144,145). The Acute Kidney Injury Network (164) has proposed a definition and classification scheme for evaluating acute kidney injury (Table 7).

Causes of acute, reversible declines in GFR should be ruled out, including dehydration, urinary obstruction or acute CNI toxicity (by demonstrating high blood levels), before a biopsy is performed. If there are no apparent causes of a decline in GFR, then an allograft biopsy is generally warranted to detect the nature of potentially treatable causes of kidney injury, including rejection, infections like BKV nephropathy, recurrent or *de novo* kidney disease or infiltration with posttransplant lymphoproliferative disease (PTLD). Since any of these conditions can develop in the setting of preexisting graft pathology, additional biopsies may be required when an abrupt change in the rate of progression is observed.

Biopsies can determine both the type and severity of immunologic damage (109). Different types of acute rejection may require different treatment approaches. For example, acute cellular rejection is usually treated with steroid pulses, but acute antibody-mediated rejection may prompt the use of specific treatments in addition to steroids.

Biopsies for a lack of improvement in graft function

When acute rejection does not respond to first-line treatment with steroids, additional treatment (e.g. with a lymphocyte-depleting antibody) may be successful (105,165). Alternatively, a failure of function to return to baseline could be due to a new pathological process, such as coexistent acute tubular necrosis, drug toxicity or BKV nephropathy, that would require a different treatment

Table 7: Diagnostic criteria for acute kidney injury

Criteria	An abrupt (within 48 h) reduction in kidney function currently defined as an absolute increase in serum creatinine of ≥0.3 mg/dL (≥26.4 μmol/L), a percentage increase in serum creatinine of ≥50% (1.5-fold from baseline), or a reduction in urine output (documented oliguria of less than 0.5 mL/kg/h for more than 6 h).
Notes	The above criteria include both an absolute and a percentage change in creatinine to accommodate variations related to age, gender and BMI, and to reduce the need for a baseline creatinine but do require at least two creatinine values within 48 h.

BMI, body mass index.
Adapted with permission (164).

approach. Therefore, a biopsy is indicated to determine the correct treatment.

Patients should always be assessed for their suitability for biopsy before undertaking the procedure. Biopsies may be hazardous in those with a bleeding diathesis, or in the presence of large fluid collections or infection.

Biopsies for DGF

Observational studies have shown that the incidence of acute rejection during DGF is higher than in patients without DGF (166–168). Kidney function cannot be used as an indication for biopsy to diagnose superimposed acute rejection while the patients are already being treated with dialysis due to DGF, or when the serum creatinine does not fall from pretransplant values. It is therefore prudent to obtain periodic biopsies of the kidney during DGF to diagnose acute rejection. There are few data to determine when and how often biopsies during DGF should be obtained. However, studies in which biopsies have been obtained every 7–10 days, while patients are receiving dialysis for DGF, have shown that acute rejection can be present for the first time on the second, third or even fourth biopsy (167).

In centers that have a very low overall incidence of acute rejection, the incidence of acute rejection during DGF could also be low enough to obviate the need for biopsies during DGF. A biopsy may no longer be needed when there are signs that DGF is resolving, for example when urine output is increasing rapidly or serum creatinine is declining.

Protocol biopsies

Acute rejection, CAI and CNI toxicity can occur in the absence of a measurable decline in kidney function. Several studies have shown that protocol biopsies can detect clinically inapparent (subclinical) acute rejection, CAI and CNI nephrotoxicity. The reported prevalence of subclinical rejection (Banff grade 1A or higher) varies from 13% to 25% at 1–2 weeks, 11–43% at 1–2 months, 3–31% at 2–3 months and 4–50% at 1 year (169–175).

Data from observational studies indirectly suggest that detecting and treating subclinical acute rejection with protocol biopsies may be beneficial. Subclinical rejection is associated with CAI (170,173,176,177) and reduced graft survival (176–179).

In another study, subclinical acute rejection in 14-day protocol biopsies was associated with poorer 10-year graft survival (179). Graft survival rates with subclinical rejection, borderline subclinical rejection or no rejection were 88%, 99% and 98% at 1 year ($p < 0.05$), and 62%, 94% and 96% at 10 years ($p < 0.05$), respectively. In a pediatric study, subclinical rejection was associated with progressive CAI, reduced creatinine clearance and shorter graft survival (177).

Treatment of subclinical rejection may improve outcomes. In a RCT, 72 patients were randomly allocated to undergo protocol biopsies and treatment of subclinical rejection at 1, 2, 3, 6 and 12 months (biopsy group), or protocol biopsies without treatment at 6 and 12 months only (control group) (100). Patients in the biopsy arm of the study had a significant decrease in acute rejection episodes, a reduced 6-month chronic tubulointerstitial score and a lower 2-year serum creatinine. Interstitial fibrosis was less in those treated for subclinical rejection (100). In another trial, 52 living-donor KTRs were randomized to undergo protocol biopsies and 50 controls had only indicated biopsies (103). At 1 and 3 months, protocol biopsies revealed borderline changes in 11.5% and 14% patients, acute rejection in 17% and 12% and CAI in 4% and 10%, respectively. The incidence of clinically evident acute rejection episodes was similar in the two groups, but the biopsy group had lower serum creatinine at 6 months ($p = 0.0003$) and 1 year ($p < 0.0001$).

Baseline immunosuppression is likely important in determining the incidence of subclinical rejection and thereby the benefit of protocol biopsies. Tacrolimus- and MMF-treated patients generally have a lower rate of acute rejection than patients treated with CsA and azathioprine, and tacrolimus is associated with a reduced incidence of subclinical rejection (104,113,176,180,181), lower acute Banff scores (182,183) and 1-year serum creatinine (181). In a RCT, 121 patients were randomly allocated to biopsies at 0, 1, 2, 3 and 6 months, and 119 to biopsies at 0 and 6 months (102). At 6 months, 35% of the biopsy arm and 20.5% of the control arm patients had interstitial fibrosis and tubular atrophy (ci + ct) scores ≥2 ($p = 0.07$). Of note, the frequency of clinical acute rejection episodes was only 10% in the biopsy arm and 7% in the control arm ($p > 0.05$). The prevalence of subclinical rejection in the biopsy arm was 4.6%. Creatinine clearance at 6 months was not different ($p > 0.05$) in the two groups. Use of protocol biopsies, therefore, for diagnosis of subclinical rejection may not be appropriate in tacrolimus- and MMF-treated patients.

Other conditions that can be detected on protocol biopsies include CNI toxicity, recurrent disease, transplant glomerulopathy, CAI and BKV nephropathy. However, it is unclear whether the detection of these conditions by protocol biopsy improves outcomes.

The safety of biopsies has been documented in several series (180,184). The reported risk of major complications from protocol biopsy, including substantial bleeding, macroscopic hematuria with ureteric obstruction, peritonitis or graft loss, is approximately 1% (185–187). The reported incidence of graft loss from protocol biopsy is 0.03%. Protocol biopsies can be done safely as an outpatient procedure. Data collected on 1705 protocol kidney transplant biopsies at one center showed that all of the complications became evident in the first 4 h after the biopsy (188).

Protocol biopsies, however, may be expensive. The Mayo Clinic reported that protocol biopsies cost US$ 3000 per biopsy, and it cost US$ 114 000 to detect one case of acute subclinical rejection (104). Therefore, decisions on whether or not to perform protocol biopsies should take these and other factors, including patient preferences, into account. Altogether, based on very-low-quality evidence, the benefit of performing protocol biopsies in CsA/azathioprine-treated patients without induction therapy may outweigh the harm (see Evidence Profile and accompanying evidence in Supporting Tables 45–47 at http://www3.interscience.wiley.com/journal/118499698/toc).

Research Recommendations

- RCTs are needed to determine when the benefits of protocol biopsies outweigh harm.