

The Banff 97 working classification of renal allograft pathology

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The Banff 97 working classification of renal allograft pathology.

Background. Standardization of renal allograft biopsy interpretation is necessary to guide therapy and to establish an objective end point for clinical trials. This manuscript describes a classification, Banff 97, developed by investigators using the Banff Schema and the Collaborative Clinical Trials in Transplantation (CCTT) modification for diagnosis of renal allograft pathology.

Methods. Banff 97 grew from an international consensus discussion begun at Banff and continued via the Internet. This schema developed from (a) analysis of data using the Banff classification, (b) publication of and experience with the CCTT modification, (c) international conferences, and (d) data from recent studies on impact of vasculitis on transplant outcome.

Results. Semiquantitative lesion scoring continues to focus on tubulitis and arteritis but includes a minimum threshold for interstitial inflammation. Banff 97 defines “types” of acute/

active rejection. Type I is tubulointerstitial rejection without arteritis. Type II is vascular rejection with intimal arteritis, and type III is severe rejection with transmural arterial changes. Biopsies with only mild inflammation are graded as “borderline/suspicious for rejection.” Chronic/sclerosing allograft changes are graded based on severity of tubular atrophy and interstitial fibrosis. Antibody-mediated rejection, hyperacute or accelerated acute in presentation, is also categorized, as are other significant allograft findings.

Conclusions. The Banff 97 working classification refines earlier schemas and represents input from two classifications most widely used in clinical rejection trials and in clinical practice worldwide. Major changes include the following: rejection with vasculitis is separated from tubulointerstitial rejection; severe rejection requires transmural changes in arteries; “borderline” rejection can only be interpreted in a clinical context; antibody-mediated rejection is further defined, and lesion scoring focuses on most severely involved structures. Criteria for specimen adequacy have also been modified. Banff 97 represents a significant refinement of allograft assessment, developed via international consensus discussions.

Key words: biopsy interpretation, allograft pathology, lesion scoring, kidney, transplantation.

Received for publication July 15, 1998
and in revised form September 18, 1998
Accepted for publication September 18, 1998

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Standardization of renal allograft biopsy interpretation and reporting is necessary to guide therapy in trans-

plant patients and to establish an objective end point for clinical trials of new antirejection agents. The Banff Working Classification of Renal Allograft Pathology is an international schema recently developed to fill this need. The classification, which originated in a meeting held in Banff, Canada on August 2 to 4, 1991, was published in 1993 [1], has been clinically validated in numerous studies [2–8], and is now widely used by center pathologists and in large international trials of immunosuppressive agents. Subsequent meetings have been held in Banff every two years to refine the classification. For National Institutes of Health clinical trials, a modification of the Banff grading system, the Collaborative Clinical Trials in Transplantation (CCTT) classification was developed; this classification and a clinical validation study were published in late 1997 [9]. This article is the report of the March 7–12, 1997, Fourth Banff Conference on Allograft Pathology, a meeting at which pathologists using the Banff schema and those using the CCTT modification met with clinical investigators to review new clinical and experimental observations on the pathology of the renal allograft, with an emphasis on mechanisms and diagnosis of rejection.

METHODS

Banff 97, the combined classification described here, is a product of an international consensus discussion begun at Banff and continued via the Internet. This modified schema for renal allograft rejection was brought about through several major influences, including (a) analysis of data from clinical trials using the Banff classification and observation of actual practice in use of the classification worldwide, (b) publication of and experience in the use of the CCTT modification [9], and (c) international consensus discussions that took place at the Second, Third [10], and Fourth Banff Conferences and at intervening meetings. In addition, data on prognosis and renal function from the Syntex/Roche mycophenolate mofetil trials [11], data from the CCTT trials [9], and a recent study focused on vascular lesions in rejection [12] have demonstrated that vasculitis of any severity has significant implications for response to therapy, and graft function and outcome, and provide a major rationale for this 1997 revision (“Banff 97”). This combined classification focuses on histologic “types” rather than “grades” of rejection. Since there are significant changes in this revised schema, there is strong incentive in many circumstances to retain the older classifications, but to incorporate Banff 97 when a new study is initiated.

RESULTS

Banff 97, presented in Table 1, represents a significant modification of the grading of acute/active rejection in

Table 1. Banff 97 diagnostic categories for renal allograft biopsies^a

1. Normal, see Definitions	
2. Antibody-mediated rejection	Rejection demonstrated to be due, at least in part, to anti-donor antibody
	A. Immediate (hyperacute)
	B. Delayed (accelerated acute)
3. Borderline changes: “Suspicious” for acute rejection	This category is used when no intimal arteritis is present, but there are foci of mild tubulitis (1 to 4 mononuclear cells/tubular cross section) and at least 1
4. Acute/active rejection	
	<u>Type (Grade)</u> <u>Histopathological findings</u>
IA	Cases with significant interstitial infiltration (>25% of parenchyma affected) and foci of moderate tubulitis (>4 mononuclear cells/tubular cross section or group of 10 tubular cells)
IB	Cases with significant interstitial infiltration (>25% of parenchyma affected) and foci of severe tubulitis (>10 mononuclear cells/tubular cross section or group of 10 tubular cells)
IIA	Cases with mild to moderate intimal arteritis (v1)
IIB	Cases with severe intimal arteritis comprising >25% of the luminal area (v2)
III	Cases with “transmural” arteritis and/or arterial fibrinoid change and necrosis of medial smooth muscle cells (v3 with accompanying lymphocytic inflammation)
5. Chronic/sclerosing allograft nephropathy ^b	
	<u>Grade</u> <u>Histopathological findings</u>
Grade I (mild)	Mild interstitial fibrosis and tubular atrophy without (a) or with (b) specific changes suggesting chronic rejection
Grade II (moderate)	Moderate interstitial fibrosis and tubular atrophy (a) or (b)
Grade III (severe)	Severe interstitial fibrosis and tubular atrophy and tubular loss (a) or (b)
6. Other	Changes not considered to be due to rejection, see Table 14.

^a The recommended format of report is a descriptive narrative signout followed by numerical codes in parentheses. Categorization should in the first instance be based solely on pathologic changes, then integrated with clinical data as a second step. More than one diagnostic category may be used if appropriate.

^b Glomerular and vascular lesions help define type of chronic nephropathy; chronic/recurrent rejection can be diagnosed if typical vascular lesions are seen.

Banff 93–95. Nonetheless, the new version retains the basic construct of the earlier schema, which includes the range of findings seen in allograft biopsies and also provides for semiquantitative grading of changes of both acute/active rejection and chronic/sclerosing allograft nephropathy. To clarify the changes made, the categorization and grading of acute changes are discussed in the context of the earlier schemas, Banff 93–95 and CCTT.

The initial modification of the schema is a change in definition of specimen adequacy. To diagnose and categorize rejection, adequate cortex must be present in the material examined, and the change has been made to ensure more adequate cortical sampling. With the new emphasis on arteritis, a more generous minimal arterial sampling is also recommended. For Banff 97, an “adequate” specimen is now defined as a biopsy with 10 or more glomeruli and at least two arteries; the threshold

Table 2. Quantitative criteria for tubulitis (“t”) score^a

t0 - No mononuclear cells in tubules
t1 - Foci with 1 to 4 cells/tubular cross section (or 10 tubular cells)
t2 - Foci with 5 to 10 cells/tubular cross section
t3 - Foci with >10 cells/tubular cross section, or the presence of at least two areas of tubular basement membrane destruction accompanied by i2/i3 inflammation and t2 tubulitis elsewhere in the biopsy

^a Applies to tubules no more than mildly atrophic

for a minimal sample is seven glomeruli and one artery. It is also recommended that at least two separate cores containing cortex be obtained or that there be two separate areas of cortex in the same core. The recommendation for slide preparation is seven slides containing multiple sequential sections, three stained with hematoxylin and eosin (HE) stain, three with periodic acid-Schiff (PAS) stain or silver stains, and one with a trichrome stain. The PAS stain and silver stains enhance the identification of glomerulitis and tubulitis and any destruction of tubular basement membranes. These stains also enhance the recognition of chronic features such as arteriolar hyaline, increased mesangial matrix, double contours in glomerular capillaries, and thickened tubular basement membranes. The trichrome stain is useful in defining interstitial fibrosis. It is recommended that histologic sections should be cut at 3 to 4 microns, as the current definitions of lesion grading are not appropriate either for 1 micron plastic sections or for “routine” thicker sections obtained at some institutions.

Acute/active lesion scoring

Semiquantitative lesion scoring provides the morphologic basis for the rejection classification. While the basic features used to diagnose rejection are tubulitis and arteritis, a minimal threshold for interstitial inflammation must be reached to diagnose rejection of the tubulointerstitial type. Glomerulitis, although not a specific criterion for rejection, may have implications for late graft function, and is also graded. Tubulitis and vasculitis, as the cardinal features of rejection, will be considered first.

The Banff 93–95 schema grades tubulitis (“t”) score based on the greatest number of infiltrating mononuclear cells in the tubular epithelium (that is, having breached the tubular basement membrane and lying beneath or between tubular cells) per tubular cross section; if the tubule is sectioned longitudinally, results are expressed per 10 tubular cells (the average number of cells per cross-section). In the CCTT modification, significant tubulitis is defined by number of tubules with tubulitis in 10 serial high-powered fields from the area with the most inflammatory infiltrate. Banff 97 retains a focus on most severely inflamed tubules to grade tubulitis and requires that the tubulitis be present in more than one focus in the biopsy (Table 2). The most inflamed tubules should

Table 3. Quantitative criteria for intimal arteritis (“v”)

v0 - No arteritis
v1 - Mild-to-moderate intimal arteritis in at least one arterial cross section
v2 - Severe intimal arteritis with at least 25% luminal area lost in at least one arterial cross section
v3 - Transmural arteritis and/or arterial fibrinoid change and medial smooth muscle necrosis with lymphocytic infiltrate in vessel

Note number of arteries present and number affected. Indicate infarction and/or interstitial hemorrhage by an asterisk (with any level v score).

be sought in the most inflamed areas in the biopsy. Inflammatory tubular injury and/or breakdown of tubular basement membranes are included as significant histologic findings in Banff 93–95 and the CCTT modification, and are included in Banff 97 in the “t3” grade. Since tubulitis is seen routinely in atrophic tubules in native kidneys and cannot be interpreted as a specific response to alloantigen, tubulitis should not be graded in moderately-to-severely atrophic tubules, that is, tubules reduced in caliber by 50% or more.

Arteritis is likewise a defining feature for rejection diagnosis in the allograft. Both Banff 93–95 and the CCTT formulations distinguish intimal arteritis, carefully defined as lymphocytic infiltration beneath the endothelium, from arteritis with inflammation in the media and/or with fibrinoid necrosis of the vessel wall. Parenchymal necrosis and/or interstitial hemorrhage were recognized as possible manifestations of severe arteritis by both classifications. Banff 93–95 vasculitis (“v”) scores focused on intimal arteritis, with v1 defined as mild-to-moderate in at least one artery, v2 as moderate-to-severe in more than one artery, and v3 as severe in many arterial cross-sections and/or with transmural arteritis, fibrinoid change, and necrosis. However, because there is the potential for significant sampling error in defining vasculitis, it was agreed that the focus of grading should be on the most severely involved vessel (analogous to tubulitis scoring). A score of v3, or severe vasculitis (v3), is now reserved for those cases with transmural arteritis and/or arterial fibrinoid change and smooth muscle necrosis with accompanying lymphocytic inflammation in the vessel (Table 3). In reporting vasculitis, the total number of arteries and the total number involved by vasculitis should be recorded. If there is interstitial hemorrhage and/or infarction, an asterisk should be added to the “v” score. Interstitial hemorrhage and/or infarction alone (that is, v0*), while raising the specter of rejection with vascular involvement not sampled by the biopsy, is no longer considered adequate to presumptively score v3.

While not itself a signal criterion for rejection, a background of interstitial inflammation is required to diagnose rejection of the tubulointerstitial type. Because minimal (and even significant) mononuclear inflamma-

Table 4. Quantitative criteria for mononuclear cell interstitial inflammation (“i”) scores

i0 - No or trivial interstitial inflammation (<10% of unscarred parenchyma)
i1 - 10 to 25% of parenchyma inflamed
i2 - 26 to 50% of parenchyma inflamed
i3 - more than 50% of parenchyma inflamed

Indicate the presence of remarkable numbers of eosinophils, PMNL, or plasma cells (specify which) with an asterisk (*).

Table 5. Quantitative criteria for early allograft glomerulitis (“g”) score

g0 - No glomerulitis
g1 - Glomerulitis in less than 25% of glomeruli
g2 - Segmental or global glomerulitis in 25 to 75% of glomeruli
g3 - Glomerulitis (mostly global) in more than 75% of glomeruli

tion is present in many protocol biopsies from asymptomatic patients, at least 10% of cortex must be inflamed as a threshold for grading of interstitial inflammation. Severe inflammation (i3) is defined when greater than 50% of the cortex is inflamed (Table 4). Areas that cannot be meaningfully graded for assessment of interstitial infiltrates are fibrotic areas, the immediate subcapsular cortex, and the adventitia around large veins and lymphatics. The infiltrate in classic cellular rejection consists of T lymphocytes and monocyte/macrophages. If there are more than 5 to 10% eosinophils, neutrophils, or plasma cells in the infiltrate, an asterisk is added to the “i” score, and other differential diagnoses should be considered, for example, hypersensitivity reaction or infection, as discussed later here. Moreover, the quality of the infiltrate must be analyzed in the context of clinical information. For example, tapering and withdrawal of immunosuppression may be followed by rejection infiltrates with a substantial component of plasma cells.

Glomerulitis is graded in both the CCTT and Banff classifications, although it is not used as a criterion for rejection since its significance has been and remains controversial. The Banff schema grades glomerulitis, defined by mononuclear cell infiltrate and endothelial cell enlargement, by the percentage of glomeruli involved and whether the process is segmental or global within involved glomeruli. In the CCTT, glomerulitis may be absent, “focal,” or “severe.” The grading of glomerulitis in Banff 97 is shown in Table 5, with g1 defined as glomerulitis in less than 25% of glomeruli and g3 as glomerulitis that is mostly global and in more than 75% of glomeruli. Polymorphonuclear leukocytes in glomerular capillaries are not a feature of transplant glomerulitis, but may be seen in antibody-mediated rejection or in early thrombotic microangiopathy.

Table 6. Overview of acute rejection

Banff 97	Banff 93–95	CCTT
Suspicious for acute rejection, borderline	Borderline	Type I ^a
Type IA (tubulointerstitial with t2 and at least i2)	Grade I	Type I ^a
Type IB (tubulointerstitial with t3 and at least i2)	Grade IIA	Type I ^a
Type IIA (vascular with v1)	Grade IIB	Type II
Type IIB (vascular with v2)	Grade III	
Type III v3 - (fibrinoid change/transmural arteritis)	Grade III	Type III

^a Additionally requires at least i1 and at least 2 of the 3 following features: edema, activated lymphocytes, or tubular injury

The Banff 97 classification: Acute/active rejection

Acute/active rejection in the Banff 93–95 schema was divided into three grades: I, mild, characterized by moderate tubulitis; II, moderate, further divided into IIa with marked tubulitis and no vasculitis and IIb with mild-to-moderate intimal arteritis; and III, severe, characterized by severe intimal arteritis or transmural arteritis or intramural necrosis. In this earlier Banff classification, recent focal infarction and interstitial hemorrhage without obvious cause could be regarded as grade III rejection. In the CCTT modification, acute/active rejection was divided into three types: I, with significant tubulitis; II, with arterial or arteriolar endothelialitis; and III, with arterial fibrinoid necrosis or transmural inflammation.

The Banff 97 classification of acute/active rejection-related changes is shown in Table 6, and is compared with rejection categories from Banff 93–95 and the CCTT modification. In view of the recent studies that provide evidence that vasculitis *per se* has implications for response to therapy and/or graft survival [9, 11, 12], Banff 97 focuses on types of rejection. Type I is tubulointerstitial rejection without arteritis, further divided into type IA with focal moderate tubulitis and IB with severe tubulitis. Type II, vascular rejection, is characterized by intimal arteritis, further divided into IIA if the intimal arteritis is mild-to-moderate, and IIB if severe. Type III, severe rejection, is with transmural arteritis with or without fibrinoid and smooth muscle necrosis. Those cases with only mild tubulitis and/or with only mild focal interstitial inflammation remain in a “borderline” category.

As in the previous working classifications, antibody-mediated rejection is also included, but now recognizing two forms, immediate (hyperacute) and delayed (accelerated acute). Except in classic hyperacute rejection occurring immediately post-transplant, antibody-mediated rejection should be confirmed by repeat cross-match, as discussed below. Antibody-mediated rejection can occur as an isolated rejection response or combined with cell-mediated rejection as an antibody-mediated component. The morphology of classic “pure” antibody-mediated

Table 7. Quantitative criteria for interstitial fibrosis (“ci”)

ci0 - Interstitial fibrosis in up to 5% of cortical area
ci1 - Mild - interstitial fibrosis in 6 to 25% of cortical area
ci2 - Moderate - interstitial fibrosis in 26 to 50% of cortical area
ci3 - Severe - interstitial fibrosis in >50% of cortical area

Table 8. Quantitative criteria for tubular atrophy (“ct”)

ct0 - No tubular atrophy
ct1 - Tubular atrophy in up to 25% of the area of cortical tubules
ct2 - Tubular atrophy involving 26 to 50% of the area of cortical tubules
ct3 - Tubular atrophy in >50% of the area of cortical tubules

rejection may be quite distinctive. In other cases, the antibody-mediated component is superimposed on cell mediated vascular changes (**Discussion**).

Lesion scoring: Chronic/sclerosing

Chronic/sclerosing changes develop in renal allograft with renal ischemia, hypertension, drug effects, infection, increased ureteral pressure, and nonimmune inflammatory processes, in addition to a subset due to chronic or recurring immune reaction to the graft [13]. Chronic changes may be seen in glomeruli, interstitium, tubules, and vessels, although not necessarily simultaneously or to the same degree. Because sampling error is less of a problem in sampling of tubules and interstitium, these features are the basis of the grading of severity of chronic allograft nephropathy. The grading of chronic interstitial fibrosis and tubular atrophy and/or loss remains unchanged from Banff 93–95, with quantitation based on the percentage of cortical parenchyma involved (Tables 7 and 8).

The grading of chronic glomerular changes related to rejection, previously defined by mesangial matrix increase and basement membrane thickening, has now been refined. The presence of “double contours” in capillary loops, created by mesangial interposition, is the most specific change of chronic transplant glomerulopathy [14], whereas mesangial matrix increase is a potentially important but less specific finding. Therefore, the two are now graded separately. Severity of chronic glomerulopathy is now graded by the extent of “double contours” in the most severely affected glomerulus. The total number of glomeruli and the total number of non-specifically sclerotic glomeruli must be recorded (Table 9). An increase in mesangial matrix is graded by the percentage of nonsclerotic glomeruli with at least moderate mesangial matrix increase. Moderate mesangial matrix increase, in turn, is defined by expansion of the matrix in the mesangial interspace between adjacent glomerular capillaries to exceed the width of two mesangial cells in at least two lobules. Grading of mesangial matrix

Table 9. Quantitative criteria for allograft glomerulopathy (“cg”)

cg0 - No glomerulopathy - double contours in <10% of peripheral capillary loops in most severely affected glomerulus
cg1 - Double contours affecting up to 25% of peripheral capillary loops in the most affected of nonsclerotic glomeruli
cg2 - Double contours affecting 26 to 50% of peripheral capillary loops in the most affected of nonsclerotic glomeruli
cg3 - Double contours affecting more than 50% of peripheral capillary loops in the most affected of nonsclerotic glomeruli

Note the number of glomeruli and percentage sclerotic.

Table 10. Quantitative criteria for mesangial matrix increase (“mm”)^a

mm0 - No mesangial matrix increase
mm1 - Up to 25% of nonsclerotic glomeruli affected (at least moderate matrix increase)
mm2 - 26–50% of nonsclerotic glomeruli affected (at least moderate matrix increase)
mm3 - >50% of nonsclerotic glomeruli affected (at least moderate matrix increase)

^a The threshold criterion for the moderately increased “mm” is the expanded mesangial interspace between adjacent capillaries. If the width of interspace exceeds two mesangial cells on the average in at least two glomerular lobules the “mm” is moderately increased.

increase (“mm” score) is shown in Table 10. Transplant glomerulopathy often also includes mesangiolysis and progressive sclerosing changes; the latter may be difficult to distinguish from membranoproliferative glomerulonephritis or, in some cases, focal segmental glomerulosclerosis.

Vascular changes potentially enable identification of kidneys with chronic/sclerosing changes due to chronic rejection. Specific chronic vascular changes that suggest that vascular changes are due to “chronic rejection” are disruptions of the elastica, best seen on special stains, and inflammatory cells in the fibrotic intima. Proliferation of myofibroblasts in the expanded intima and formation of a second “neointima” are also useful features [15, 16]. Fibrointimal thickening in vessels without these features is a significant finding, especially if it is of new onset and is graded, but it is not regarded as specific for “chronic rejection.” Recognizing that vascular changes may be focal, chronic vascular changes are graded based on the extent of occlusion of the most severely affected vessel (Table 11).

Finally, arteriolar hyaline change, particularly if nodular and documented to be of new onset, may be an important manifestation of cyclosporine or FK506 toxicity [17], as discussed later here, and has a separate lesion scoring in the schema. The scoring of this lesion remains unchanged from Banff 93–95 (Table 12). Arteriolaritis is a lesion that is currently of uncertain significance; if present, it is designated by an asterisk added to the “arteriolar hyalinosis” (“ah”) score.

Because it is often impossible to define the precise

Table 11. Quantitative criteria for vascular fibrous intimal thickening ("cv")

cv0 - No chronic vascular changes
cv1 - Vascular narrowing of up to 25% luminal area by fibrointimal thickening of arteries \pm breach of internal elastic lamina or presence of foam cells or occasional mononuclear cells ^a
cv2 - Increased severity of changes described above with 26 to 50% narrowing of vascular luminal area ^a
cv3 - Severe vascular changes with >50% narrowing of vascular luminal area ^a

^a In the most severely affected vessel. Note if lesions characteristic of chronic rejection (breaks in the elastica, inflammatory cells in fibrosis, formation of neointima) are seen.

Table 12. Quantitative criteria for arteriolar hyaline thickening ("ah")

ah0 - No PAS-positive hyaline thickening
ah1 - Mild-to-moderate PAS-positive hyaline thickening in at least one arteriole
ah2 - Moderate-to-severe PAS-positive hyaline thickening in more than one arteriole
ah3 - Severe PAS-positive hyaline thickening in many arterioles

Indicate arteriolitis (significance unknown) by an asterisk on ah.

cause or causes of chronic allograft damage, the term "chronic/sclerosing allograft nephropathy" is preferable to "chronic rejection," which implies allogeneic mechanisms of injury, unless there are specific features to incriminate such a rejection process. However, recognition of those cases that do represent "chronic/recurrent rejection" may be important, as there are preliminary data suggesting that therapy may be efficacious in these cases [18]. In chronic/sclerosing allograft nephropathy, grades 1 (mild), 2 (moderate), and 3 (severe), as mentioned earlier here, may be modified by "a" (no changes strongly suggestive of chronic rejection in glomeruli and/or vessels present) or "b" (changes strongly suggestive of chronic rejection present (Table 1). If convincing diagnostic features are present, a diagnosis of "chronic/recurrent rejection" can be made.

The Banff 97 combined working classification

The Banff 97 combined classification of renal allograft pathology includes acute/active rejection, chronic/sclerosing allograft nephropathy, and other morphologic findings, including *de novo* and recurrent diseases, toxic changes, and infection (Tables 1 and 13). Major changes from the previous Banff schema are summarized in Table 14.

DISCUSSION

The Banff 97 Working Classification represents input from the two classifications most widely used in large clinical rejection trials and in clinical practice worldwide to diagnose acute rejection. This new international classi-

Table 13. Other non-rejection diagnoses in renal allograft biopsies

Post-transplant lymphoproliferative disorder
Nonspecific changes
focal interstitial inflammation without tubulitis
reactive vascular changes
venulitis
Acute tubular necrosis
Acute interstitial nephritis
Cyclosporine or FK506-associated changes, acute or chronic
Subcapsular injury
"healing in "
Pretransplant acute endothelial injury
Papillary necrosis
<i>De novo</i> glomerulonephritis
Recurrent disease
immune complex glomerulonephritis
focal segmental glomerulosclerosis
diabetes
hemolytic-uremic syndrome
other
Pre-existing disease
Viral infection
Obstruction/reflux, urine leak
Other

fication follows earlier classifications that took the approach of semiquantitative grading of rejection lesions to provide an acute rejection index. Finkelstein et al published such a classification in 1976, in the pre-cyclosporine era [19]. This classification graded interstitial inflammation, glomerulitis, and arteritis; intimal arteritis and tubulitis were not recognized separately. Mild rejection had interstitial inflammation; moderate and severe rejection were characterized by vasculitis. Banfi et al published a similar classification in the same era [20], recognizing an irreversible form of rejection with large artery changes and infarction. In 1983, Matas et al proposed a schema with eight grades, the first four defined by minimal-to-severe tubulointerstitial nephritis, categories 5 through 7 defined by minimal-to-moderate vasculitis, and category 8 reserved for cases with severe vascular rejection with fibrinoid necrosis [21]. These grades showed a general correlation with survival, although numbers in some of the categories were too small to draw firm conclusions.

Several studies have concluded that the presence of vasculitis in a renal allograft biopsy is associated with poorer response to therapy and/or outcome. For example, Visscher et al found that in cases with steroid-resistant rejection, the response to OKT3 was lower in those with vascular injury (arteritis and/or chronic changes) [22]. Vasculitis (intimal arteritis \pm fibrinoid necrosis) has also been reported to impact negatively on allograft survival [23]. In a pediatric series, all of those with vasculitis (mostly severe) lost their allograft [2]. While a deleterious impact of vasculitis on rejection outcome has not been a uniform finding [19], three very recent studies,

Table 14. Changes from Banff 93, 95^a

<u>Lesion scoring - Acute</u>	
severity of vasculitis is based on most severely involved vessel	
moderate vasculitis (v2) is now severe intimal arteritis (more than 25% luminal occlusion)	
severe vasculitis (v3) now requires inflammatory changes in muscle wall	
interstitial hemorrhage and/or necrosis is no longer sufficient to grade v3	
threshold for grading interstitial inflammation is more than 10% of non-scarred cortical parenchyma	
<u>Lesion scoring - Chronic</u>	
transplant glomerulopathy (cg) is now defined by “double contours”	
cg now graded by severity in most involved glomerulus	
chronic vascular changes (cv) now flagged as due to chronic rejection if characteristic changes seen	
mesangial matrix increase (mm) now scored separately	
<u>Combined schema</u>	
antibody-mediated rejection replaces “Hyperacute rejection” and is further defined	
acute rejection now defined as “types”: I, tubulointerstitial; II, vascular; and III, severe	

^a Asterisks now are used to denote unusual cell composition of interstitial infiltrates (1*), presence of hemorrhage and/or necrosis (v*), and arteriolitis (ah*).

summarized briefly later here, reach a conclusion similar to these earlier studies, and have led to the Banff 97 categorization of acute/active rejection changes as “types” (tubulointerstitial or vascular) rather than “grades” of rejection.

The Roche mycophenolate mofetil study [11] included 87 biopsies scored blinded to clinical history or outcome using the Banff criteria. The highest tubulitis and vasculitis scores in the biopsy/biopsies obtained post-transplant from each case, as defined by the Banff 93–95 grading system, were recorded. The finding of vasculitis of any grade was significantly correlated with allograft loss. Outcome, defined by graft survival, was independent of rejection therapy cohort.

In a study of the modified Banff grading system used in the CCTT [9], in which type I rejection is defined by tubulointerstitial inflammation, type II by intimal arteritis, and type III by arterial necrosis or transmural inflammation, there was a significant correlation of these patterns with severity of clinical rejection. Clinically severe rejection was defined in these protocols as a rejection episode that was steroid resistant, treated with ATG, OKT3, or FK506, or was of early onset, occurring within 10 days of transplantation. The odds ratio for severe rejection was 6.2 for Type I and 37.9 for Type II. Since this classification does not provide semiquantitative grading of severity of individual inflammatory changes, no correlations with severity of inflammatory changes were defined, except that extent of tubulitis or interstitial infiltrate did not correlate with severity.

In a more recent study, Nicleleit et al analyzed the prognostic significance of vascular lesions in rejection [12]. They found that rejection with endarteritis was sig-

nificantly less responsive to steroid therapy than rejection without endarteritis. One-year graft failure was also somewhat higher in the group with arteritis (28%) than without (21%), although the difference was not significant. Conversely, severity of interstitial inflammation and tubulitis (defined by CCTT criteria) did not correlate with response to therapy or outcome.

The threshold for rejection diagnosis is an important component of any diagnostic grading system. It is clear that some inflammatory changes are to be expected in any allograft, but do not necessarily signal rejection. Examination of protocol biopsies in asymptomatic patients has revealed that, in some cases, significant interstitial inflammation may be present [24, 25]. This observation led to a de-emphasis of interstitial inflammation in establishing a diagnosis of rejection in both the Banff and CCTT classifications. Similarly, mild tubulitis, defined in the Banff schema as no more than four inflammatory cells in the most inflamed tubule, has been documented in biopsies from well-functioning allografts as well and is, therefore, not included as a criterion for rejection.

Rush et al established a protocol in which they biopsied asymptomatic patients at intervals post-transplant [26]. Using Banff criteria, they found that approximately one-third of these patients had “subclinical rejection,” that is, i2t2 with a less than 10% change in serum creatinine. Patients randomized to early protocol biopsies and treatment of this “subclinical rejection” had a significantly lower creatinine at 24 months than those patients randomized to the control arm [27]. This finding suggests that the threshold of i2t2 for the diagnosis of rejection is likely appropriate, even in those cases with no change in serum creatinine, since untreated chronic graft injury may result.

The significance of “borderline” rejection [mild tubulitis (t1) only, or focal tubulitis with only mild interstitial inflammation (i1)] has been difficult to define. If mild tubulitis, as defined by the Banff criteria, was included as a criterion for rejection in the study by Rush et al, over 50% of the patients would have subclinical rejection, likely leading to unnecessary increase in immunosuppressive therapy. A few studies have looked at this “borderline” cohort. In some series, patients with borderline rejection usually responded to antirejection therapy; however, the finding of borderline changes with mild tubulitis does not always correlate with clinical rejection as defined by response to therapy [28–30]. In some centers, biopsies are obtained after treatment is initiated so that inflammatory changes may have diminished in individuals that did indeed have a significant rejection episode; in this circumstance, i1t2 lesions may, in fact, have clinical significance as an indicator of rejection. It is clear that these mild inflammatory changes can only be adequately interpreted in a clinical context; borderline changes in biopsies obtained in the context

of decreased function may require therapy, whereas borderline changes in protocol biopsies performed on patients with stable graft function may not [30]. Possible diagnoses for this category include the following: suspicious for acute rejection, borderline for acute rejection, borderline inflammatory changes only, possible (early) acute rejection, probable (early) acute rejection. The final designation may depend on center experience, therapy, time after transplant, and other clinical and morphological features, including other signs of inflammatory cell activation or tissue injury.

The criteria for rejection diagnosis in the CCTT modification included tubulitis plus two of the following three criteria: interstitial edema, activated lymphocytes (or blasts), or tubular injury. However, on evaluation of the individual pathologic criteria for rejection, removal of these three additional criteria resulted in reclassification of only two cases, one that responded to antirejection therapy and one that did not [9]. Moreover, in those centers in which biopsy is frequently performed after steroid bolus therapy, edema and activated lymphocytes are much diminished within one to two days. These additional criteria, however, may occasionally be useful when combined with other morphologic findings and in clinical context in those cases with borderline changes [31].

Type I and type II rejection are both thought to be manifestations of cell-mediated rejection. However, type II may be seen in and type III is strongly suggestive of an antibody-mediated component to the rejection process. Other pathologic features suggesting an antibody-mediated component have been identified in cases in which antidonor antibody has been identified [32, 33]. These features include widespread endothelial injury with more severe vasculitis (frequently accompanied by fibrinoid changes in the vessel walls), glomerular and small vessel thromboses, infarctions, glomerulitis, marginating cells, and especially polymorphonuclear leukocytes, in peritubular capillaries. When these features are prominent, the biopsy findings should be graded according to the Banff criteria, and the possibility of an antibody-mediated rejection component should be indicated as well. The presence of antibody-mediated rejection should be confirmed by a repeat donor-specific cross-match.

Banff 97 also includes grading of chronic/sclerosing change in renal allograft biopsies. This remains an important component, as most allografts are now lost to often slowly evolving and clinically indolent sclerosis in the allograft. Recognizing that the tubulointerstitial changes are most accurately sampled and have the strongest correlation with outcome in native as well as allograft kidneys [34], the grading of severity of chronic rejection continues to focus on interstitial fibrosis and tubular atrophy and loss. However, identification of distinctive vascular changes may enable the diagnosis of chronic rejection, which in turn may be amenable to therapy [18]. The other

major grading system that focuses on chronic changes is the Chronic Allograft Damage Index (CADI), which provides semiquantitative assessment of a number of chronic and inflammatory features that have been validated as clinically relevant predictors of allograft outcome [35]. The CADI and the Banff schema have been adjusted to provide equivalent information.

It must be emphasized that although rejection-related changes are a focus of the Banff 97 schema, there are a number of other disease processes that may involve the allograft and must be considered in the differential diagnosis (Table 13). Those processes that produce inflammatory changes in the allograft must be differentiated from acute rejection. Polymorphonuclear leukocytes (PMNL) in the interstitium and especially in tubular lumina may signal acute bacterial infection, although they may be seen in cases in which there is significant ischemic injury and infarction (which may in turn be rejection related). If PMNL are confined to peritubular and glomerular capillaries, the possibility of severe acute endothelial injury and possible antibody-mediated rejection must be considered. While numerous eosinophils may be a feature of the inflammatory response to alloantigen, the possibility of a hypersensitivity reaction must be in the differential as well.

Viral infections must always be considered, as inflammatory infiltrates in this setting are typically mononuclear, and significant tubulitis may be seen. The specimen should be examined carefully for evidence of viral cytopathic features such as megalic cells, nuclear smudging, or intranuclear or cytoplasmic inclusions. If the clinical or pathological index of suspicion is high, immunohistology or *in situ* hybridization can be used to enhance identification of viral agents. Cytomegalovirus [36], polyoma (BK) virus [37], and adenovirus [38] may all infect the allograft. Colvin believes that relatively severe tubular cell injury with relatively mild inflammation should suggest the possibility of a viral infection [39]. Infection may, of course, coexist with rejection, making diagnosis and therapy problematic.

Plasma cells may likewise be a component of the rejection response, but may also signal infection. If the plasma cells are part of an aggressive infiltrate, that is expanding and displacing normal structures, and especially if the cells are atypical, post-transplant lymphoproliferative disorder (PTLD) must be ruled out. The separation of renal Epstein-Barr virus (EBV)-associated PTLT from severe acute rejection at biopsy remains very important, as the appropriate treatment is reduction of immunosuppression for PTLT, but aggressive anti-T-cell therapy for severe rejection. Potential differential features have been identified [40]. PTLT typically shows expansile or nodular mononuclear infiltrates with irregular foci of serpiginous necrosis. PTLT lesions may be focal or diffuse, and the latter may result in extensive involvement

of the pericalyceal adipose tissue and nerves. The infiltrates in PTLD generally show the entire spectrum of lymphocyte differentiation, including immunoblasts, plasma cells, large cleaved/noncleaved cells, and small round lymphocytes. Cells with marked nuclear atypia are usually present and help in the differential diagnosis from rejection. Some biopsies have a monotonous appearance, and such patients may be histologically and clinically indistinguishable from intermediate-to-high grade lymphomas in nonimmunocompromised patients.

Although they are not as readily found as in severe rejection, PTLD cells can also be associated with tubulitis. Of course, rejection and PTLD can coexist in a biopsy [41], making accurate diagnosis especially difficult. In most cases, and especially with limited biopsy material, the final diagnosis must await the results of immunophenotyping, and EBV *in situ* hybridization. With rare exceptions, PTLD lesions are B-cell preponderant and EBV positive, whereas rejection is associated with a primarily T-cell infiltrate, which is EBV negative. CD20 (B-cell marker) and CD3 (T-cell marker) immunohistochemistry is a reliable way of phenotyping infiltrates in formalin-fixed material. The most sensitive technique for demonstrating EBV in routinely processed tissue is *in situ* hybridization for EBV-encoded small RNA [42]. In lesions with significant numbers of plasma cells, staining for kappa and lambda light chains is a convenient way of identifying lesions that are clearly clonal. If sufficient fresh tissue is available, immunoglobulin gene rearrangement and oncogene studies should also be performed, as molecular findings have also been related to ultimate prognosis [43].

Toxic effects of cyclosporine and of tacrolimus also remain important differential considerations. Toxic effects of cyclosporine have been studied for some time, but tacrolimus is a relatively new agent, and its toxicity profile is still being defined. Cyclosporine and tacrolimus share a closely related mechanism of action, which is paralleled by an overlap in the toxicity profile of these two drugs. The pathology of tacrolimus nephrotoxicity appears to be similar to cyclosporine toxicity [44–47], although it has been much less completely studied. Tubular vacuolization is the most common finding in biopsies performed during clinical episodes of tacrolimus nephrotoxicity; tubular vacuoles may be seen in proximal as well as distal tubules, and although these are often isometric, focal coalescence into larger vacuoles is also present. As with cyclosporine, tacrolimus therapy may also be associated with microvascular toxicity characterized by damage to the glomerular capillaries and renal arterioles. Arteriolar damage mediated by tacrolimus sometimes results in an acute arteriopathy characterized by endothelial swelling, mucoid intimal thickening, eosinophilic globules in the media, and focal medial necrosis. Scattered thrombi may be seen in capillary loops or afferent arterioles. Prolonged tacrolimus therapy results in arteri-

olar hyaline eosinophilic deposits comprised of fibrin, IgM, C3, and C1q, which may be difficult to distinguish from those due to aging, hypertension, and diabetes mellitus. As with CsA, arteriolar myocyte vacuolization can be seen; this lesion is a nonspecific manifestation of vessel spasm and should be ascribed to tacrolimus toxicity only after exclusion of other causes of vessel injury. Drug-induced vasospasm and the hyalinization of the interlobular arteries and arterioles may lead to ischemic injury accentuated in the medullary rays and probably also the medullary inner stripe [48], leading to striped or diffuse interstitial fibrosis.

Significant tubulointerstitial inflammation or vasculitis may also be components of recurrent or *de novo* renal disease in the allograft. These differential considerations must be considered at any time post-transplant and become more likely as time post-transplant increases. A good pretransplant clinical history can be invaluable in considering differential diagnoses.

Finally, future advances in analysis of renal allograft biopsies can already be predicted, and the classification and grading of acute/active rejection will continue to evolve. The significance of specific morphologic findings—including glomerulitis, arteriolitis, and infiltrates with unusual cellular features—for acute and chronic allograft function and outcome will continue to be investigated. Emphasis in biopsy assessment will shift from diagnosis to prediction of later allograft function and outcome, potentially enabling early intervention. Indeed, two recent studies have shown that chronic histologic changes detected in early protocol biopsies and graded using the 93–95 Banff schema were predictive of long-term outcome [49, 50]. Clinical utility of renal allograft biopsies, for both diagnosis and prediction of outcome, will be enhanced by application of immunostaining and molecular studies. Identification of effector cells such as NK cells and cytotoxic T-lymphocytes and of monocyte/macrophages may enhance diagnosis and/or predict later dysfunction. Molecular studies show promise in refining the diagnosis of acute/active rejection [51], although much more needs to be done to establish validity in cases with borderline features and to disseminate the technology. It will be important to establish which molecular markers correlate with interstitial infiltrates and which correlate with invasive inflammation (tubulitis, intimal arteritis). Also, more precise definition of histologic and molecular features of indolent graft injury and sclerosis should enable better understanding of pathogenesis of progressive damage and enable appropriate therapy. There is clearly much work to be done in optimizing the assessment of the renal allograft by the pathologist as we move into the 21st century. Many of these issues will receive focused attention at the Fifth Banff Conference on Allograft Pathology in 1999 and in other international forums, which have become logical venues for such consensus in the global medical community.

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