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Meeting Report

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Banff '09 Meeting Report: Antibody Mediated Graft Deterioration and Implementation of Banff Working Groups

B. Sis[a,b,*], M. Mengel[a,b], M. Haas[c], R. B. Colvin[d], P. F. Halloran[b], L. C. Racusen[e], K. Solez[a], W. M. Baldwin III[f], E. R. Bracamonte[g], V. Broecker[h], F. Cosio[i], A. J. Demetris[j], C. Drachenberg[k], G. Einecke[l], J. Gloor[i], D. Glotz[m], E. Kraus[n], C. Legendre[o], H. Liapis[p], R. B. Mannon[q], B. J. Nankivell[r], V. Nickeleit[s], J. C. Papadimitriou[k], P. Randhawa[j], H. Regele[t], K. Renaudin[u], E. R. Rodriguez[v], D. Seron[w], S. Seshan[x], M. Suthanthiran[y], B. A. Wasowska[e], A. Zachary[n] and A. Zeevi[j]

[a] *Department of Laboratory Medicine and Pathology,*
[b] *Alberta Transplant Applied Genomics Centre, Division of Nephrology & Immunology, Department of Medicine, University of Alberta, Edmonton, Canada*
[c] *Department of Pathology and Laboratory Medicine, Cedars-Sinai Medical Center, Los Angeles, CA*
[d] *Department of Pathology, Harvard Medical School and Massachusetts General Hospital, Boston, MA*
[e] *Department of Pathology, Johns Hopkins University, Baltimore, MD*
[f] *Department of Immunology, Lerner Research Institute, Cleveland Clinic, OH*
[g] *Department of Pathology, University of Arizona, Tucson, AZ*
[h] *Department of Pathology, Hannover Medical School, Germany*
[i] *Division of Nephrology and Hypertension, The Mayo Foundation and Clinic, Rochester, NY*
[j] *Division of Transplantation Pathology, Department of Pathology, University of Pittsburgh, Pittsburgh, PA*
[k] *Department of Pathology, University of Maryland, Baltimore, MD*
[l] *Department of Nephrology, Hannover Medical School, Germany*
[m] *Department of Nephrology, Hospital Saint-Louis, Paris, France*
[n] *Department of Medicine, John Hopkins University, Baltimore, MD*
[o] *Université Paris Descartes & Service de Transplantation, Hôpital Necker, Paris, France*
[p] *Department of Pathology and Immunology, Washington University School of Medicine, St Louis, MO*
[q] *Division of Nephrology, University of Alabama, Birmingham, AL*
[r] *Center for Transplant Research and Renal Research, Westmead Hospital, Sydney, Australia*
[s] *Department of Laboratory Medicine and Pathology, University of North Carolina, Chapel Hill, NC*
[t] *Institute for Pathology, University of Vienna, Vienna, Austria*
[u] *Department of Pathology, CHU Hotel Dieu, Nantes, France*
[v] *Department of Anatomic Pathology, Cleveland Clinic, Cleveland, OH*
[w] *Department of Nephrology, Hospital Vall d'Hebron, Barcelona, Spain*
[x] *Department of Pathology and Laboratory Medicine, Weill Cornell Medical College, New York-Presbyterian Hospital, New York, NY*
[y] *Division of Nephrology, Department of Medicine, Weill Medical College of Cornell University, New York, NY*
[*] *Corresponding author: Banu Sis, bsis@ualberta.ca*

The 10th Banff Conference on Allograft Pathology was held in Banff, Canada from August 9 to 14, 2009. A total of 263 transplant clinicians, pathologists, surgeons, immunologists and researchers discussed several aspects of solid organ transplants with a special focus on antibody mediated graft injury. The willingness of the Banff process to adapt continuously in response to new research and improve potential weaknesses, led to the implementation of six working groups on the following areas: isolated v-lesion, fibrosis scoring, glomerular lesions, molecular pathology, polyomavirus nephropathy and quality assurance. Banff working groups will conduct multicenter trials to evaluate the clinical relevance, practical feasibility and reproducibility of potential changes to the Banff classification. There were also sessions on quality improvement in biopsy reading and utilization of virtual microscopy for maintaining competence in transplant biopsy interpretation. In addition, compelling molecular research data led to the discussion of incorporation of omics-technologies and discovery of new tissue markers with the goal of combining histopathology and molecular parameters within the Banff working classification in the near future.

Key words: Acute allograft rejection, acute cellular rejection, acute rejection, allograft rejection, antibody mediated rejection, Banff, Banff lesions, Banff schema, classification, chronic allograft rejection, donor specific antibody, genomic markers, GeneChip, heart allograft, microarrays, proteomics, pancreas allograft, transplantation

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Introduction

The 10th Banff Conference on Allograft Pathology was held in Banff, Canada from August 9 to 14, 2009. A total of 263 transplant clinicians, pathologists, surgeons, immunologists, and researchers from more than 30 countries discussed several aspects of solid organ transplants with a special focus on alloantibody responses, role(s) of endothelial cells in rejection, noninvasive markers of rejection, genomics/proteomics approaches, and updates on kidney, pancreas, heart, liver, lung and composite tissue graft pathology.

A major topic of discussion was detrimental effects of antibodies on allografts and related phenotypes. Antibody-mediated rejection (ABMR) in various organs including related mechanisms, phenotypes, prognostic factors and clinical management were extensively discussed in the light of new studies.

An initiative stimulated by premeeting surveys was implementation of Banff working groups (BWGs) to address problematic issues in allograft pathology. In addition, initiatives for implementing an organizational structure and Banff training courses for transplantation pathology were set. This report reviews meeting content and summarizes current status of the BWGs. Outcomes of BWGs will be published separately and presented in future meetings.

ABMR: An underestimated problem in allografts

Robert Colvin (Boston) reviewed the history of ABMR. Although detrimental roles of antibodies were first recognized in late 1960s, the link to graft pathology remained unrecognized for decades (1,2). In the early 1990s, clinicopathologic observations led to the recognition of histopathological features of acute ABMR in kidney (3,4), followed by discovery of C4d staining (5). After another decade, late graft losses due to antibody and pathologic features of chronic ABMR related to C4d and donor specific antibodies (DSA) were recognized (6,7).

Dr. Colvin emphasized that animal models of pure ABMR are still lacking. It was shown that murine cardiac transplant vasculopathy can be induced by either complement-activating (8,9) or noncomplement activating DSA (10–12). Similarly, Gary Hill (Paris) reported acceleration of arteriosclerosis in protocol biopsies from DSA+ patients, when compared with DSA-patients.

Andrea Zachary (Baltimore) reviewed antibody detection and monitoring in transplantation. Solid phase assays have high sensitivity and specificity compared to cell-based assays, but various substances in serum can interfere. Further, there is huge variability in quantitative antibody measurements between different institutions and between detection platforms. Therefore, careful standardization and establishment of clinically relevant thresholds are critical for accurate assessment of results. Factors affecting monitoring schedules include extent of sensitization, highly immunogenic mismatches, immunosuppressive protocols and posttransplant events, i.e. *de novo* antibodies or increased strength of preexisting antibody. Recently, Locke et al. (13) showed that posttransplant pro-inflammatory events such as trauma or infections are associated with increased antibody production. Further, a novel test for detection of donor-reactive antiendothelial antibodies by flow cytometric cross-match assay (XM-ONE) using peripheral blood endothelial progenitor cells is now available (14). A multicenter study related positive XM-ONE crossmatches to increased rejection among patients lacking anti-HLA DSA (14).

Maria Gerbase de Lima (Sao Paolo) reported that there are ongoing multicenter studies on minor histocompatibility antigen mismatches in HLA-identical renal transplants, MICA antibodies and antiendothelial antibodies in renal transplantation. A multicenter study in more than 4000 patients by Paul Terasaki and coworkers demonstrated significantly reduced 1- and 4-year graft survival in kidney (15), heart, lung (16), but not liver allografts with *de novo* anti-HLA DSA.

Mark Stegall (Rochester) reported that ABMR was associated with high DSA levels in positive cross-match (+CM) patients and protocols aimed at maintaining DSA at lower levels may decrease the incidence of ABMR (17). He presented initial results using anti-C5 antibody to prevent ABMR in 10 +CM patients: Protocol biopsies and antibody monitoring up to 1-month posttransplant showed no ABMR so far. Hao Wang (London, Ontario) reported that anti-C5 with conventional immunosupression prevented both ABMR and cellular rejection in presensitized murine transplants, and prolonged graft survival (18).

ABMR occurs in various organ allografts

ABMR occurs not only in kidneys, but also in heart, lung, pancreas and rarely liver allografts (19).

A full-day heart session was devoted to ABMR in partnership with the international society for heart and lung transplantation and was attended by 60 immunologists, pathologists and cardiologists. The incidence of ABMR in heart transplants is estimated as approximately 5% (20). However, current criteria for diagnosing cardiac acute ABMR lack standardization of definitions and grading of lesions, require acute graft dysfunction and more importantly, depend on screening by histology (21). Two large surveys revealed that there is no standardization on ABMR criteria and how to interpret C4d staining, including C4d positivity with no dysfunction. A premeeting trial initiated by

Dr. Rodriguez showed that C4d and C3d immunohistochemistry in endomyocardial biopsies among centers is reproducible. The attendees reached consensus recommending specific time points to monitor DSA as well as C4d (and if feasible C3d) staining on every cardiac allograft biopsy; interpreting C4d staining only in myocardial capillaries and scoring as diffuse (>50% of capillaries), focal (<50%) or negative, but accepting only diffuse staining as positive. A large study correlated C4d and C3d with allograft dysfunction, DSA and high mortality, whereas C4d alone correlated with the expression of complement regulators and no dysfunction (20).

The pancreas group also revisited the criteria for diagnosis of ABMR. The initial recommendation of doing C4d staining in all biopsies in order to identify interacinar capillary staining was reiterated. Erika Bracamonte (Tucson) presented initial results of ongoing reproducibility studies of grading cell mediated pancreas rejection using Banff schema. Revisions of ABMR criteria in heart and pancreas allografts will be published separately. Definition of ABMR in lung allografts, however, still needs further work.

Role of endothelium, platelets, and Fc receptors in ABMR

Banu Sis (Edmonton) emphasized that ABMR is dominated by endothelial damage in microcirculation, which may be mediated by complement and leukocytes via complement and/or Fc receptors. Microarray studies indicated that endothelial gene expression in kidney transplant biopsies with DSA detects ABMR and predicts poor graft survival (22). Increased endothelial transcripts also identified 30 C4d negative grafts that manifest features of ABMR including DSA, transplant glomerulopathy (TG), interstitial fibrosis and tubular atrophy (IFTA) and increased graft loss, suggesting that these cases represent C4d negative ABMR. Only 40% of kidneys with high ENDAT expression and chronic ABMR or graft loss was diagnosed by C4d positivity. Thus high ENDAT expression with antibody predicts graft loss with higher sensitivity (77% vs. 31%) and slightly lower specificity (71% vs. 94%) than C4d.

Wink Baldwin (Cleveland) discussed effector functions of antibodies. The sugar moiety in the Fc portion modifies antibody function: Fc sialylation reduces IgG cytotoxicity, whereas agalactosylated IgG activates Fc receptors and the complement pathway via mannose-binding lectin (23), potentially contributing to inflammation and injury. The Baldwin group showed that antibody to class I can trigger endothelial exocytosis of von Willebrand factor (vWF) *in vitro* in the absence of complement, but this requires F(ab')2 or the cross-linking of the Fab portions (24).

Barbara Wasowska (Baltimore) discussed the involvement of Fc/Fc receptor interaction in ABMR. IgG1 allo-mAbs to class I antigens augment graft injury by stimulating endothelial cells to produce monocyte chemoattractant protein 1 and by activating mononuclear cells through their Fc receptors (25). Further, in the absence of Fcγ RIII the lack of effective clearance of apoptotic cells leads to enhanced inflammation, complement deposition, antibody production and accelerated graft rejection (26).

Wink Baldwin also discussed important roles for platelets in ABMR. His group utilized a mouse skin transplant model in which alloantibody induces platelet activation and rolling *in vivo* (27). Repeated IgG2a alloantibody injections resulted in vWF release, small platelet thrombi, and complement deposition. Furthermore, platelets recruit leukocytes to sites of alloantibody deposition and sustain leukocyte–endothelial cell interactions *in vivo*.

T. Mohanakumar (St. Louis) discussed the role of anti-HLA induced autoimmunity in lung allografts. Mouse lung allografts receiving anticlass I showed increased chemokines and autoantibodies, and IL-17 blockade reduced autoantibody levels and obliterative airway lesions (28). However, It is yet unknown whether autoantibodies are important in clinical transplant rejection. He also presented a preliminary study suggesting that erythrocyte- bound C4d by flow cytometry correlates with DSA, autoantibodies and C3d positivity in lung allograft, and may serve as a screening test for ABMR in the lung.

C4d and graft pathology

Banu Sis reviewed relationship of TG to C4d and antibodies, and concluded that the majority of TG represents late ABMR (29–31). She reported that 70% of 53 TG biopsies had anti-HLA (mostly class II DSA), 36% C4d staining, 91% capillary multilayering, 90% arterial fibrosis, 70% peritubular capillaritis and 35% glomerulitis (29). However, only 53% of TG with alloantibody showed C4d, suggesting that C4d staining has low sensitivity for chronic ABMR. Furthermore, TG kidneys with increased endothelial gene expression showed accelerated graft loss after biopsy diagnosis whether there was C4d or not, however, TG with no endothelial stress showed good survival (32).

Brian Nankivell (Sydney) reported early electron microscopic findings in longitudinal analysis of protocol biopsies from recipients who later developed TG (33). Ultrastructural changes were seen as early as 1-month posttransplant including endothelial thickening and vacuolation, subendothelial accumulation of electron lucent material and basement membrane multilayering, followed by mesangial matrix increase. Thus routine electron microscopy evaluation may optimize earlier diagnosis of this prognostically important lesion.

Mark Haas (Los Angeles) reported findings from C4d+ biopsies with no evidence of rejection (34). In protocol biopsies from ABO-incompatible grafts, 21/37 had C4d+ antibody+ with no ABMR or T-cell-mediated rejection (TCMR) lesions. At 1-year, aggregate chronicity score was

lower in C4d+ grafts with no histologic lesions of rejection, perhaps a form of accommodation. The long-term significance and applicability of these results to conventional allografts remain unknown. On the other hand, James Gloor (Rochester) emphasized that accommodation in +CM kidneys is unlikely as many develop TG (35).

Phenotyping late kidney transplant deterioration

Roslyn Mannon (Alabama) reviewed causes and final pathways leading to IFTA. Regardless of the insult, IFTA is the final common pathway following progressive injury (36). Michael Mengel (Edmonton) reported that IFTA is associated with a distinct pattern of inflammatory molecules, including B cell/immunoglobulin and mast cell-associated transcripts, which correlated with poor outcomes (37). Further, fibrosis genes, i.e. collagens and TGF-beta are increased in IFTA biopsies, but also increased during acute injury, indicating a dynamic process between healing and scarring.

Fernando Cosio (Rochester) reported that 15% of 1317 conventional kidney transplants showed death-censored graft loss in approximately 4-year follow-up, and 98% of these failures were attributable to specific causes (38). Glomerular pathologies (36%) caused the largest proportion of graft losses, of which 15% was due to recurrent glomerulonephritis and 15% due to TG (38). Thus contrary to common beliefs, most kidney graft losses have an identifiable cause that is not idiopathic IFTA or calcineurin-inhibitor toxicity.

John Papadimitriou (Baltimore) presented glomerular lesions in biopsies from 239 kidney transplants and reported that TG was the third common (13%) glomerular finding and had the worst survival in comparison to other glomerular pathologies.

Phil Halloran (Edmonton) reported phenotypes of late failed grafts in a prospective study of 173 conventional kidney transplants (39): Banff diagnoses did not explain many losses. However, when microcirculation lesions and HLA-antibody were used to define ABMR, 63% of late kidney failures were attributable to antibody-mediated microcirculation injury; many were C4d negative, suggesting that detection of this phenotype requires new diagnostic criteria. Glomerulonephritis accounted for 22% of late losses. Thus data from two centers independently indicated that TCMR, drug toxicity and unexplained scarring were uncommon causes.

Arthur Matas (Minneapolis) reported preliminary data from the multicenter Deterioration of Kidney Allograft Function study (DEKAF), which examines troubled kidney allografts. Using clustering methods, investigators identified six prognostic clusters of biopsies by Banff scores. They also showed that C4d staining and inflammation in atrophic areas are associated with worse survival. Similary, M. Suthanthiran (New York) emphasized that mRNA expression signatures in the urine may predict the status of the allograft and may help to diagnose/prognosticate rejection, and to develop mechanism-based therapies.

Molecular phenotype of kidney transplant biopsies

Phil Halloran summarized lessons from the Edmonton transcriptome project. Transcriptome changes in kidney allograft biopsies are highly stereotyped: single molecules move in large 'herds' and analyzing them by comparing sick versus normal produces largely predictable, thus trivial results. He emphasized that molecular studies and outcome analyses must be disease-specific. Jeff Reeve (Edmonton) reported that microarray studies largely validate the Banff criteria for rejection (40). Disagreement occurred in approximately 20% of diagnoses, principally because of threshold levels in the Banff schema. The problematic diagnosis of 'borderline rejection' was resolved by gene classifier into two distinct classes, rejection and nonrejection. Areas where the Banff schema is problematic are; borderline, C4d negative ABMR, and interpretation of arteritis with little or no tubulo-interstitial inflammation (=isolated v-lesions). Stimulated by these findings the respective BWGs will address the unmet needs of the classification. In regards to C4d negative ABMR, the simultaneous presence of DSA and high endothelial gene expression in biopsy tissue may serve as a sensitive and specific method (22), but needs validation and standardization (i.e. which transcripts, platform and thresholds) across multiple centers.

Updates from the 2007 Banff Conference

Parmjeet Randhawa (Pittsburgh) and Helen Liapis (St. Louis) discussed clinical relevance of focal C4d staining in renal allograft biopsies (41,42). In both studies, 38% or 69% of focal C4d cases had DSA, respectively. In the study by immunofluorescence, there was a trend towards worse graft survival with focal C4d+, but this was not significant. As suggested by Banff 2007 C4d scoring, focal C4d on paraffin was associated with increased lesions of ABMR.

Michael Mengel presented the significance of total inflammation (ti) score in renal allograft biopsies. Compared with i- and t-scores, ti-score better reflects molecular phenotype of the tissue (43). The prognostic value of the ti-score was significant even in grafts with scarring, in which the i-score lost its prognostic value. The ti-score was also better predictor of outcome than Banff diagnoses except ABMR. The diagnostic and prognostic value of the ti-score should now be validated by different centers before it is added to the Banff schema.

Verena Broecker (Hannover) presented a clinico-pathologic study of arteriolar hyalinosis in renal allograft biopsies, employing the 2007 proposed alternative grading for arteriolar hyalinosis (aah) (44,45). Arteriolar lesions were not correlated with trough levels of calcineurin-inhibitors or blood pressure, but aah was common in grafts from older donors,

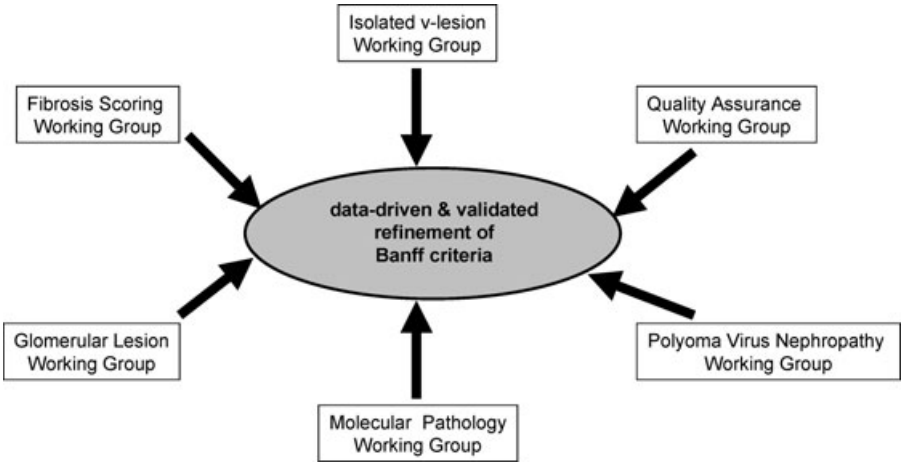

Figure 1: Established Working Groups at the Banff 2009 meeting aiming at addressing current unmet needs within the Banff classification to support or refute potential changes to the classification via conducting multicenter trials.

emphasizing the need for baseline (0-time) biopsies for differentiating the potential etiologies of arteriolar lesions in subsequent renal allograft biopsies. The reproducibility of the aah-score are yet to be validated by different groups.

Christophe Legendre (Paris) reviewed the utility of 0-time biopsies. Notably, in the United States ∼16% of recovered deceased donor kidneys were not transplanted; in ∼50% of cases this decision was made based on a donor kidney biopsy. At Dr. Legendre's center, the decision was based on donor serum creatinine, donor hypertension, and% globally sclerotic glomeruli in 0-time biopsies. These criteria were predictive of graft performance (46). Still, a uniform approach to 0-time biopsies is clearly desirable in order to optimize the value of such biopsies in decision-making at the time of transplantation.

Banff working groups

Six BWGs aiming at addressing unmet needs in transplantation pathology were established (Figure 1). These international BWGs will collect data on areas where Banff criteria are problematic, work with multiple centers, validate the results, and ultimately refine and improve the classification, thus ensuring that the Banff process is evidence-based and continues to lead to improvements in patient care and management.

Isolated v-lesion: Banu Sis and Edward Kraus reviewed ongoing work aimed at addressing the significance of isolated v- lesions in renal allograft biopsies. Such lesions are characterized by arteritis with minimal interstitial inflammation (i $\leq$1) and tubulitis (t $\leq$1). However, some of these lesions were not associated with expression of gene sets for T cells, interferon-gamma and tissue injury (47), and are thus of uncertain significance. At present, 144 biopsies with isolated v-lesions have been collected from seven centers. Work will soon commence comparing outcomes of patients with isolated v-lesions with control groups. During the meeting, inclusion and exclusion criteria were modified and more centers enrolled in the study.

Fibrosis scoring: Dr. Colvin reported the results of a pre-meeting survey, which showed significant variability in fibrosis scoring among pathologists. As this is an important surrogate end point, the participitants planned reproducibility trials to standardize fibrosis scoring.

Polyoma virus nephropathy staging (PVN)

Volker Nickeleit (Chapel Hill) proposed a classification of PVN that includes three stages, modified from histologic patterns of PVN reported by Drachenberg et al. (48): stage-A (early changes, without tubular epithelial cell necrosis); stage-B (active nephropathy with virally induced tubular necrosis) and stage C (late sclerosing changes). The proposal was approved by consensus with pending trials to ensure the reproducibility of the new PVN staging.

Glomerular lesion scoring

Mark Haas proposed a multicenter trial to re-examine scoring double contours (cg), glomerulitis (g) and mesangial matrix increase (mm) aiming at refinement of these criteria to increase the interobserver reproducibility.

Molecular pathology

The group led by Phil Halloran will facilitate the consensus about how and which molecular markers can be integrated into the Banff classification. RT-PCR or chip (with few genes) based molecular measurements may be incorporated into the existing histology-based Banff classification and/or discovery of new diagnostic and/or prognostic tissue markers could be feasible with the help of omics technologies.

Quality assurance

This group will plan Banff training courses, proficiency tests, and immunohistochemistry (C4d and BK) multicentre staining trials.

These ongoing projects and consensus discussions will be detailed in separate publications. Transplant physicians

Table 1: Banff 97 diagnostic categories for renal allograft biopsies—Banff '09 update

1. Normal
2. Antibody-mediated changes (may coincide with categories 3, 4 and 5 and 6)
   Due to documentation of circulating antidonor antibody, C4d,[1] and allograft pathology
C4d deposition without morphologic evidence of active rejection
   C4d+, presence of circulating antidonor antibodies, no signs of acute or chronic TCMR or ABMR (i.e. g0, cg0, ptc0, no ptc lamination (<5 layers by electron microscopy), no ATN-like minimal inflammation). Cases with simultaneous borderline changes are considered as indeterminate
Acute antibody-mediated rejection[2]
   C4d+, presence of circulating antidonor antibodies, morphologic evidence of acute tissue injury, such as (Type/Grade)
   I. ATN-like minimal inflammation
   II. Capillary and or glomerular inflammation (ptc/g >0) and/or thromboses
   III. Arterial – v3
Chronic active antibody-mediated rejection[2]
   C4d+, presence of circulating antidonor antibodies, morphologic evidence of chronic tissue injury, such as glomerular double contours and/or peritubular capillary basement membrane multilayering and/or interstitial fibrosis/tubular atrophy and/or fibrous intimal thickening in arteries
3. Borderline changes: 'Suspicious' for acute T-cell mediated rejection (may coincide with categories 2 and 5, and 6)
   This category is used when no intimal arteritis is present, but there are foci of tubulitis (t1, t2 or t3) with minor interstitial infiltration (i0 or i1) or interstitial infiltration (i2, i3) with mild (t1) tubulitis
4. T-cell mediated rejection (TCMR, may coincide with categories 2 and 5 and 6)
Acute T-cell mediated rejection (Type/Grade:)
   IA. Cases with significant interstitial infiltration (>25% of parenchyma affected, i2 or i3) and foci of moderate tubulitis (t2)
   IB. Cases with significant interstitial infiltration (>25% of parenchyma affected, i2 or i3) and foci of severe tubulitis (t3)
   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 with accompanying lymphocytic inflammation (v3)
Chronic active T-cell mediated rejection
   'chronic allograft arteriopathy' (arterial intimal fibrosis with mononuclear cell infiltration in fibrosis, formation of neo-intima)
5. Interstitial fibrosis and tubular atrophy, no evidence of any specific etiology
   (may include nonspecific vascular and glomerular sclerosis, but severity graded by tubulointerstitial features)
   Grade
   I. Mild interstitial fibrosis and tubular atrophy (<25% of cortical area)
   II. Moderate interstitial fibrosis and tubular atrophy (26–50% of cortical area)
   III. Severe interstitial fibrosis and tubular atrophy/ loss (>50% of cortical area)
6. Other: Changes not considered to be due to rejection- acute and/or chronic (For diagnoses see table 14 in (49); may include isolated g, cg, or cv lesions and coincide with categories 2, 3, 4, and 5)

ATN, acute tubular necrosis.
The 2009 updates are underlined. All existing scoring categories (g, t, v, i, ptc, cg, ct, ci, cv, ah, mm) remain unchanged (45, 49).
[1]Please refer to Banff 2007 classification paper (45).
[2]Suspicious for antibody-mediated rejection if C4d (in the presence of antibody) or alloantibody (C4d+) not demonstrated in the presence of morphologic evidence of tissue injury.

from around the world are encouraged to participate in the BWGs (http://cybernephrology.ualberta.ca/Banff/).

Erratum to Banff 07 Classification of Renal Allograft Pathology (45)

Presence of acute tubular necrosis was reported as indeterminate for 'C4d deposition without morphologic evidence of active rejection'. It is now corrected that the criteria for this diagnosis will be (i) C4d staining in peritubular capillaries, (ii) lack of histologic evidence of acute or chronic rejection (cellular or humoral) with lack of glomerulitis, TG, peritubular capillaritis, peritubular capillary basement membrane lamination (assessed by electron microscopy <5 layers) and acute tubular necrosis, (iii) presence of DSA (Table 1).

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