Review Article

Banff Classification from 1991 to 2019. A Significant Contribution to Our Understanding and Reporting of Allograft Renal Biopsies

Abstract

The Banff schema of classification of renal allograft biopsies, first proposed at the meeting in Banff, Canada in 1991 has evolved through subsequent meetings held once in two years and is the internationally accepted scheme of classification which is consensual, current, validated and in clinical use. This review traces the evolution of the classification and our understanding of renal transplant pathology, with emphasis on alloimmune reactions. The proceedings of the meetings and the important studies which have shaped the classification are covered.

Keywords: *Allograft biopsy, Banff, rejection*

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Introduction

The first meeting was held at the city of Banff in Canada in August 1991, of an international group of Pathologists, Nephrologists, Surgeons with a common interest in Renal transplantation with a task to standardise reporting of renal allograft biopsies. The first report was published in 1993 after several cross consultations. Subsequent meetings have been held every two years across the world but have been christened the Banff meetings and our understanding of graft pathology in general and rejections in particular have evolved with discussions and publications arising out of these meetings. The Banff schema is unique as the criteria are decided based on a consensual discussion. They are based on scientific studies and publications and it continues to remain modern, and continuously updated.

Purpose of the Review

This review has outlined the developments in each of the Banff categories beginning 1991, reviewed the important studies which shaped the classification and the temporal sequence of events leading to the latest 2019 update. As students of Medicine and Nephrology, it is important that we understand the rationale of the present classification, the studies which have shaped it and do not just recognise it as a series of names and numbers which need to be remembered for the examination and reporting. It is fascinating to note that some categories like antibody-mediated rejection (ABMR) have undergone a sea change since the first meeting whereas other categories like borderline are still poorly understood.

The first meeting in 1991: A series of follow-up meetings, correspondence and circulation of sets of glass slides followed the first Banff meeting in 1991 leading to the Banff working classification of kidney transplant pathology which was published in 1993.[1] At the very first meeting, the patterns of injury were classified as acute in the form of glomerulitis (g), interstitial inflammation (i), tubulitis (t), and intimal arteritis (v) and chronic in the form of chronic glomerulopathy (cg), interstitial fibrosis (ci), tubular atrophy (ct), arteriolar hyalinosis (ah) and intimal fibrosis (ci). Each of these was assigned scores 0 to 3 based on objective criteria. The recognition of other patterns of injury evolved with the meetings and today, there are 18 Banff scores and their evolution is given in Table 1.

Six categories numbered 1 to 6 were:

1. Normal
2. Hyperacute rejection
3. Borderline changes
4. Acute rejection
5. Chronic allograft nephropathy (CAN) and
6. Changes not considered to be due to rejection.

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Table 1: Evolution of the Banff scores

Year of meeting	Acute scores*	Chronic scores*	Acute and chronic scores*
'91[1]	g, i, t, v, ah (quantitative for i3 and t3 only)	cg, ci, ct, cv	
'97[4]	Quantitative criteria for g, i, t, v, ah	Quantitative criteria for cg, ci, ct, cv mm introduced	
'07[23]	Quantitative criteria for ptc, C4d, aah		Quantitative criteria for ti
'13[39]		cg1 divided into cg1a and 1b	
'15[41]		Quantitative criteria for ptcml by EM	Quantitative criteria for i-IFTA
'19[32]			Quantitative criteria for t-IFTA and pvl

aah-hyaline arteriolar thickening, ah-arteriolar hyalinosis, cg-glomerular double contours, ci-interstitial fibrosis, ct-tubular atrophy, cv-vascular fibrous intimal thickening, EM0-electron microscopy, g-glomerulitis, i-inflammation in non-scarred cortex, i-IFTA-inflammation in areas of interstitial fibrosis and tubular atrophy, mm-mesangial matrix expansion, ptc-peritubular capillaritis, ptcml-peritubular capillary basement membrane layering, pvl-polyoma viral load, t-tubulitis, ti-total inflammation in scarred and non-scarred cortex, t-IFTA-tubulitis in areas of interstitial fibrosis and tubular atrophy, v-intimal arteritis. *All scores graded from 0 to 3

Categories 1 and 6 have remained unchanged. The evolution of the remaining categories, from 1991 to 2019, will be discussed below. The guiding philosophy of the classification was to keep false positives low and recognise that terminologies like acute and chronic rejections as well as the criteria for these were bound to change with growing knowledge.

Category 2: In the first meeting in 1991, hyperacute rejection was the only recognised entity in this category, mediated by pre-existing antibodies.[1] By the second publication in 1997, this was recognised as antibody-mediated rejection (ABMR) and was considered to be of two types—type 1, the immediate or hyperacute, and type 2, the delayed (accelerated acute), confirmed by a repeat cross match.[2] Historically, two great Peters championed the study of rejections, Peter Gorer on antibody-mediated and Peter Medawar on cell-mediated rejections. Due to the untimely demise of Prof Gorer, the study of ABMR suffered a setback for more than a decade before it was brought to the forefront. The main thrust of the 2001 meeting and the '2001 update of the '97 classification', which was published in 2003 was antibody-mediated rejection.[3]

Phil Halloran in the early'90s and Trypkov a little later had shown glomerulitis, presence of neutrophils in peri-tubular capillaries (PTC) and fibrin thrombi in grafts to be associated with antibodies against donor class I Human Leucocyte Antigen (HLA) antigens and proposed that this was an entity distinct from classic acute rejection and hyperacute rejection.[4-6] K. Moruzomi *et al.* from Japan confirmed similar changes in ABO-incompatible grafts.[7]

The seminal publication by Feucht *et al*. showed that capillary deposition of C4d, a terminal component of the complement cascade, correlated with graft survival (1-year graft survival 64% in those with C4d deposition and 90% in those without).[8] C4d deposition was also more commonly seen in those with Type II rejection, namely those with vessel changes.[9] Collins *et al.*, in their study,[10] were the first to show a clear correlation of C4d positivity with the presence of donor specific antibodies (DSA) and certain histologic features and this paved the way for the introduction of criteria for diagnosing ABMR in the Banff schema. Crespo *et al.* showed that 37% of their steroid resistant rejection had DSA and C4d was positive in 95% of them. Besides, acute tubular injury (ATN) was the only histologic manifestation in 10% of these cases and hence, this was included in the injury pattern of ABMR.[11]

In the large study by Nickeleit *et al.*,[12] about 18% of the C4d positive group had no histologic features of rejection and their follow-up was not different from the C4d negative group. Thus, C4d positivity alone was not sufficient for diagnosis of ABMR and further criteria were required. Regele *et al.*[13] showed a high specificity and low sensitivity for C4d positivity when compared to DSA. Two methods of demonstration of C4d on tissues, namely immunofluorescence (IF) and immunohistochemistry (IHC) with the former being more sensitive were developed around the same time.

In the 2001 update, with inputs from the above studies, 3 sets of criteria were mandated for a conclusive diagnosis of acute ABMR:

1. Morphologic evidence of tissue injury (type I- ATN with minimal inflammation, type II—inflammation within PTC, glomeruli and/or thrombi, type III—intimal arteritis/fibrinoid necrosis/transmural inflammation)
2. Evidence of antibody action—C4d in PTC walls/Ig and complement in arterial fibrinoid necrosis
3. Evidence of anti HLA/anti-endothelial DSA.

If criterion 3 was not shown, a diagnosis of 'suspicious of ABMR' was given

By 2005, there was also accumulating literature on the existence of chronic rejections both T-cell and antibody -mediated. These criteria were incorporated in the '05 Banff update.[14] Thus emerged the diagnostic criteria for chronic active ABMR which were:

1. Morphologic evidence of chronic injury: Transplant glomerulopathy (TG) (duplication/double contours of

glomerular basement membrane)/peritubular capillary basement membrane multilayering shown by electron microscopy (EM)/tubular atrophy with or without PTC loss/fibrous intimal thickening without elastosis
2. Evidence of antibody action—C4d in PTC walls
3. Evidence of anti HLA/anti-endothelial antibodies DSA.

If the morphologic injury was seen with only criterion 2 or 3, it was labelled as 'suggestive of chronic ABMR'.

Refinements of the criteria and scores for diagnosis of ABMR continued to evolve at the 2007 meeting.[15] The inter-observer reproducibility of peritubular capillaritis (ptc) was moderate[16] and ptc was also found to be predictive of peri-tubular capillary basement membrane lamination on follow-up by Lerut *et al*.[17] ptc scoring, proposed in 2005 was incorporated. With regard to C4d, though diffuse C4d positivity (>50%) was significant, the significance of focal staining was not clear. Besides, IF was more sensitive than IHC and this needed to be adjusted. Focal C4d by IHC was found to correlate with glomerulitis/ptc in a large study by Mengel *et al*.[18] The criterion for C4d positivity was finalised with the consensus that ≥10% positivity in the PTC walls on IHC and ≥50% positivity on IF was reported positive.

The diagnosis 'C4d positivity without morphologic evidence of active rejection' was introduced under the category of ABMR where the histology was normal but C4d and DSA were positive. It was felt that the outcome in this group may not be benign and a follow up was advocated.[19]

Even at the 10th meeting in 2009, discussions on ABMR continued to occupy centre stage.[20] Endothelial activation and injury with expression of endothelial transcripts (ENDATS) was a manifestation of ABMR and high ENDAT expression predicted graft loss with higher sensitivity than C4d.[21] Majority of TG represented chronic ABMR.[22,23] Although majority of chronic ABMR with ENDATs had C4d positivity, only 53% of TG with alloantibody were C4d positive. These studies paved the way for recognition of C4d negative ABMR and identification of specific gene transcripts as an alternative to C4d detection was gaining ground.

By 2011 it was recognised that C4d positivity, though specific for ABMR had limited sensitivity due to the methodology (IF vs IHC), presence of non-complement fixing antibodies, waxing and waning of C4d deposition and reduced capillary density.[24] A new working group was established to define the criteria for C4d negative ABMR which would include defining thresholds for i) microvascular injury ii) C4d negativity iii) acute vs chronic active ABMR and iv) significance of intimal arteritis.

At the 12th meeting in 2013, the recommendations for diagnosing C4d negative acute/active (previously termed only acute) and chronic ABMR were finalised.[25] The criteria were:

1. Morphologic evidence of AMR. Intimal arteritis was included in active ABMR
2. Evidence of current/recent antibody interaction with vascular endothelium: C4d positivity (defined as score ≥1 by IHC and >1 by IF).
   When C4d was negative, microvascular inflammation (g+ptc) ≥2 or increased expression of a validated ENDAT were the alternative criteria.
3. Serologic evidence of DSA (HLA or non-HLA).

The definitions of score 1 glomerulitis, TG and C4d positivity were also revised to include very early lesions as they correlated with ENDAT and DSA selective gene transcript profile.[26,27]

At the 13th meeting held in 2015, it was decided that C4d deposition in PTC walls was predictive of presence of DSA. Grafts with C4d deposition, irrespective of the presence of DSA had similar outcome. As the diagnosis of ABMR required all three criteria, it was recommended that where criteria 1 and 2 were fulfilled, the report would read 'Suspicious of ABMR; expedited DSA testing advised'.[28]

At the subsequent meeting in 2017, a need for an alternative to the DSA criterion was felt as the test was not readily available and the current testing methods did not detect all DSAs.[29] As C4d positivity was highly specific for ABMR, this was considered an alternative to the DSA criterion. DSA specific transcripts or an alternative ABMR molecular classifier was also considered an alternative to DSA[30,31] DSA testing was however still strongly recommended for risk stratification, evaluating response to therapy and for patient monitoring.

The word 'acute' was removed from acute/active ABMR as the reaction could be subacute or smouldering in nature and the term 'active ABMR' was to be used to denote ongoing disease activity.

At the most recent meeting in 2019,[32] as there still seemed to be some confusion in the minds of physicians about how and when to treat chronic active ABMR, it was recommended that the severity of the activity and chronicity depending on the Banff scores be mentioned in the diagnostic line. A diagnosis of chronic ABMR (inactive) could be rendered when the biopsy had morphologic changes but C4d was negative and there was a remote DSA positivity prior to the biopsy.

Category 3: This category, borderline changes suspicious of rejection was envisaged at the very first meeting for those cases with interstitial inflammation and tubulitis not meeting the criteria for acute rejection. At the 2005 meeting, borderline changes suspicious of acute TCMR was extended to include i0, namely no or minimal inflammation.[14] Till the last meeting in 2019, there were no changes in the criteria. In 2019, the diagnostic criterion

for i was reverted to at least i1 (inflammation in ≥10% of cortex),[32] as longitudinal studies by Nankivell *et al.*[33] had shown no effect of isolated 't' on allograft survival.

Category 4: At the first meeting, tubulitis and endarteritis were recognised as important features of acute rejection. Inflammation, though important was recognised as not specific for rejection, variable and subject to sampling errors.[34] Acute rejection was graded I, II and III depending on the severity of tubulitis and the vessel changes.

Independent diagnostic criteria had been published by the NIH sponsored Cooperative Clinical Trials in Renal Transplantation (CCTT)[35] where three types of rejection—tubulointerstitial, vascular and humoral were recognised and they were not graded. The CCTT had a lower threshold for diagnosing rejections. These two schemes were fused and the consensus published as the Banff '97 classification.[2]

The other advance in '97 was the recognition that vasculitis of any severity impacted the severity of acute rejection and had implications for therapy and prognosis.[36] Acute rejection was named acute/active and graded into three types—type I, namely tubulo-interstitial graded into Ia and Ib depending on the severity of tubulitis and type II when there was intimal arteritis, divided into 'a' and 'b' depending on the severity of arteritis and type III with transmural arteritis. Interstitial haemorrhage and/or infarction alone (v0), mentioned in the '93 categories was no longer adequate for diagnosis of severe rejection and does not find a mention in any of the further Banff schema.

In the 2001 update, the acute/active rejection was renamed acute/active cellular rejection to contrast it from ABMR. It was also recognised that isolated endarteritis could be the only manifestation of a severe rejection.[3]

At the 2005 meeting, acute/active cellular rejection was finally christened T-cell-mediated rejection (TCMR), in contrast to ABMR, emphasising the two distinct arms of alloimmune injury.[14] If transplant arteriopathy was present without the other changes of chronic ABMR, and without criteria 2 or 3 of ABMR mentioned above, it was chronic TCMR.

By 2007, studies had shown that inflammation even in areas of atrophy impacted graft outcome and also had an increased expression of rejection gene sets.[37,38] Total infiltrate score (ti) which scored inflammation in scarred and no-scarred areas was introduced.

The consensus on the isolated 'v' lesions was that most represented type 2 TCMR. However, 11% and 13% of them were associated with anti-class I and class II HLA antibodies, respectively. Some of these may therefore represent acute ABMR or a mixed TCMR and ABMR.

Interest in chronic transplant arteriopathy which since then was considered a manifestation of chronic TCMR surfaced with the finding by Loupy *et al.*[39] that they could be seen in chronic active ABMR too. Besides, changes of chronic TCMR in the experimental model involved the tubulo-interstitial compartment.[40] As interstitial inflammation in atrophic areas (i-IFTA) was associated with decreased graft survival,[41,42] it was recommended that i-IFTA be included in the Banff scores and scored similar to i score.

The DeKaf study showed a strong correlation of iIFTA with graft loss, stronger than with IFTA alone.[42] This was validated by similar studies by Lefaucheur *et al.*[43] and Nankivell *et al.*[44] The latter study also showed that iIFTA is typically preceded by TCMR. iIFTA was felt to be a pattern of acute injury warranting therapy. Though not specific for rejection, when accompanied by tubulitis with a history of TCMR and when other conditions like infections were excluded, iIFTA with tubulitis was indicative of a chronic active TCMR. The criteria for chronic active TCMR, grades IA, Ib and II, similar to acute TCMR were laid out.

At the 2019 meeting,[32] there was a fine tuning of the diagnostic criteria and reporting formats for rejections. In a biopsy with chronic active TCMR, if the i score (inflammation in non-scarred areas) criterion for acute or borderline TCMR was met, then the diagnostic line would read combined chronic active TCMR and acute/borderline TCMR aiding the decision about anti-rejection therapy.

Category 5: Chronic allograft nephropathy (CAN) even in 1991 was recognised as not specific of etiology.[1] In the '97 update CAN was graded into I, II and III grades depending on the severity with the comment that they were suggestive of rejection when accompanied by corresponding glomerular and large vessel changes.[2] Chronic rejections though recognised, did not exist then as a separate category.

In the Banff 2005 meeting report,[14] the important development was the elimination of the term 'CAN', as CAN was being considered a specific diagnosis when in fact it was just a non-specific pattern of chronic injury which could be due to rejections (alloimmune-mediated) or due to non-immune injury including hypertension, calcineurin inhibitor (CNI) toxicity, chronic obstruction, pyelonephritis, viral infection, de-novo and recurrent disease. When all of the above non-immune causes were excluded by a careful study of the biopsy, the ancillary tests and the clinical history, one could resort to a diagnosis of 'interstitial fibrosis and tubular atrophy (IFTA), of no specific type', and this was graded according to the severity as earlier.

Evolution of Molecular Diagnostics

At the 2005 meeting, a symposium on molecular approaches and techniques heralded the incorporation of an

omics approach to the Banff classification. Assays at that time were however not robust for clinical use but the ball had been set rolling to bring in a molecular approach to advance the Banff system.

By 2015, the inadequacy of a system based only on microscopy was recognised and attempts were made to integrate molecular diagnostics, the first being ENDATs which was incorporated as a criterion for diagnosis of C4d negative ABMR. For molecular diagnostics, standards for platforms, methods and reproducibility were essential. The INTERCOM studies[45] was set to assess the molecular microscope approach in graft biopsies and to compare the gene expression classifiers. Analogous to the Banff consensus process for morphologic lesions in 1991, the key areas for developing consensus in molecular diagnostics was for i) Indication (diagnosis/prediction/treatment monitoring) ii) Application (tissue biopsies/body fluids) iii) Targets (RNA, miRNA, free DNA, protein) iv) Platforms (PCR/microarray/ELISA etc). More collaborative multicentre studies were required to fill the knowledge gaps, arrive at a consensus on gene sets which could be validated with hard clinical end points, before they could be put into routine clinical use.

At the 2017 meeting, molecular diagnostics were recommended in situations where a combination of histologic, immunologic and serologic data was inconclusive. The publication had the table enlisting the differential diagnoses and the possible molecular tests which could be done in different clinical scenarios.[29]

Banff Working groups (BWG)

As progress was happening on multiple fronts, Banff working groups (BWG) were formed in 2009. The mandate of these groups was to conduct clinical trials and evaluate the relevance, practical feasibility and reproducibility of introducing changes to the classification. Six working groups were initially formed to study isolated 'v' lesions, fibrous scoring, glomerular lesions, molecular pathology, polyoma virus nephropathy and quality assurance. These working groups became a routine feature in subsequent meetings with groups created to address TCMR, clinical and laboratory assessment of highly sensitised recipients, evaluation of molecular diagnostics, etc., Digital pathology, machine learning and artificial intelligence heralding the era of automated Banff classification has been the latest BWG proposed in 2019. These groups continue to bring value to the classification by working in select areas and proposing validated modifications.

Table 2 lists the key developments in categories 2 (antibody-mediated changes), category 4 (T-cell-mediated rejection) and category 5 (IFTA). Categories 1 (normal) and category 6 (changes other than rejection) remain unaltered.

Table 2: Evolution of the Banff schema

Meeting, year	Category 2°	Category 4°°	Category 5°°°
Pre-Banff	Hyperacute	Acute	Chronic
Banff '93[1]	-do-	Acute, grades I, II, III	CAN*, grades I, II, III
Banff '97[2]	Hyperacute	Acute/active cellular	-do-
	Accelerated acute	Types IA/B, IIA/B, III	
'97 update[3]	ABMR**, types I, II, III	-do-	-do-
Banff '05[14]	ABMR-acute, chronic	TCMR***—acute, chronic active^	IFTA of no specific etiology, grades I, II, III
	Set of 3 criteria		
Banff '07[15]	-do-	-do-	-do-
	C4d without rejection		
Banff '13[25]	ABMR-acute/active,	-do-	-do-
	chronic active		
	C4d negative ABMR		
Banff '15[28]	Suspicious for ABMR if DSA negative	Chronic active TCMR may have tubulo-interstitial changes	-do-
	Transplant arteriopathy may be seen in chronic ABMR		
Banff '17[29]	3 criteria for ABMR diagnosis remains but C4d can substitute for DSA.	Chronic active TCMR grades I A/B and II defined	-do-
	DSA testing still advised	i-IFTA included in criteria^^^	
Banff '19[32]	In chronic active ABMR, severity of activity and chronicity to be mentioned	In chronic active TCMR with i>1, diagnosis to be combined chronic active and acute TCMR	Grading of polyoma viral nephropathy into classes 1, 2 and 3^^^^
	Chronic ABMR defined^^		

°Antibody mediated changes °°T-cell-mediated °°°Interstitial fibrosis and tubular atrophy. *Chronic allograft nephropathy**Antibody mediated rejection ***T-cell-mediated rejection. ^Includes only transplant arteriopathy ^^Chronic without activity ^^^inflammation in areas of atrophy ^^^^ Adequate sample for scoring should include 2 cores with medulla

Conclusions

The story of the Banff classification is a long one spanning nearly three decades. It is a story of consensus building, relying on scientific evidence, one that is constantly evolving, incorporating new technology and with emphasis on clinical application. It is important that as students of Medicine and Nephrology, we do not view the classification as a mere table of lesions and numbers, but understand the historical evolution and the basis for the schema

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