PERSPECTIVE REVIEW

Development of Banff Classification from 1991 to 2019 for identifying renal allograft rejection: A narrative review for nephrologists

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Abstract

Renal pathologists, nephrologists and transplant surgeons held a meeting in 1991 at Banff, Canada, and developed a classification scheme that standardised the international classification of renal allograft biopsies and called it the Banff Classification. Following the first meeting, 15 meetings were held, usually every two years, that revised the classification in the light of new evidence and techniques. The latest printed consensus was after the 2019 meeting in Pittsburgh in the United States of America. Several articles have been published in the last 30 years that have created ambiguities for nephrologists and have made things challenging for the expert pathologists. The current perspective review was planned to make it easy and clear for beginners and for practitioners how the Banff Classification has evolved since its inception.

Keywords: Development, Banff classification, Renal allograft rejection.

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Introduction

Before the Banff Classification, which in 1991 standardised the international classification of renal allograft biopsies at a meeting in Banff, Canada, renal allograft rejection was typically classified into the following 04 forms:[1] Hyper-acute, which meant rejection occurs due to pre-existing antibodies usually within minutes; Acute, which meant rejection after 5-7 days because of activated T cells; Accelerated acute, which meant rejection <5 days in pre-sensitised individuals, usually as a result of pregnancy, blood transfusion or a prior transplant; Chronic, which was defined as gradually worsening graft function beginning 3 months post-transplant.

Although a few classifications for rejections were present but were hardly in general use.[2] Because of reporting variability in the description of renal graft biopsies, a new standardised classification was needed.

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Renal pathologists, nephrologists, and transplant surgeons held a meeting at Banff and developed a standardised international classification of renal allograft biopsies which was published in March 1993.[3] It not only had international consensus, but provided help in making a clinical diagnosis, and also permitted a judgment between research studies and clinical trials that investigated either the diagnosis, treatment or outcome in renal transplantation.[4] Thereafter, the Banff group has been meeting biannually, last meeting being the 15th Banff Conference for Allograft Pathology held September 23-27, 2019, in Pittsburgh, the United States of America.[5] Because new knowledge and techniques have been many and frequent, there have been many revisions of the classification. This has resulted in the Banff Classification of Allograft Pathology becoming the main classification system accepted all over the world[6]. Following the first meeting in 1991, 15 meetings were held, usually every two years, which produced 13 articles till the last published consensus after the 2019 meeting in Pittsburgh.[3,5,7-17]

The 13 articles published may have created some confusion in nephrologists and pathologists, and a clear understanding of renal allograft rejection is of great significance not only for research but also in clinical practice. The current perspective review was planned to make it easy and clear to both the beginners and the practising nephrologists how the classification evolved since its inception.

First Banff 1993: The first Banff Classification was published in 1993,[3] and defined that more than seven glomeruli with at least one artery and having seven slides: 3 Haematoxylin and Eosin (H&E), 3 Periodic acid-Schiff (PAS), and 1 Manson's trichrome. This was defined as adequate.

It also outlined categories 'Borderline Changes' and 'Chronic Allograft Nephropathy' (CAN); and graded 'acute rejection' into mild, moderate, and severe. Graft biopsies were classified into six categories: Normal, Hyper-acute rejection, Borderline, Acute rejection, CAN, and Other (Table-1).

Also introduced was a numerical grading system for each

Table-1: Diagnostic categories for renal allograft biopsies (Banff 1993).[3]

1. Normal
2. Hyperacute rejection
Characterized by presence of thrombi in the microvasculature, interstitial haemorrhages, and prominence of neutrophils in the glomeruli
3. Borderline changes ("very mild acute rejection")
This category is used when no intimal arteritis is present, but only mild or moderate focal mononuclear cell infiltration with foci of mild tubulitis (1 to 4 mononuclear cells/tubular cross section).
4. Acute rejection
Grade I, mild acute rejection
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).
Grade II, moderate acute rejection
Cases with (A) significant interstitial infiltration and foci of severe tubulitis (> 10 mononuclear cells/tubular cross section) and/or (B) mild or moderate intimal arteritis.
Grade III, severe acute rejection
Cases with severe intimal arteritis and/or "transmural" arteritis with fibrinoid change and necrosis of medial smooth muscle cells. Recent focal infarction and interstitial haemorrhage without other obvious cause are also regarded as evidence for Grade III rejection.
5. Chronic allograft nephropathy
(Glomerular and vascular lesions help define type of chronic nephropathy; new-onset arterial fibrous intimal thickening suggests the presence of chronic rejection.)
Grade I - Mild, chronic transplant nephropathy Mild interstitial fibrosis and tubular atrophy
Grade II - Moderate chronic transplant nephropathy Moderate interstitial fibrosis and tubular atrophy
Grade III - Severe chronic transplant nephropathy Severe interstitial fibrosis and tubular atrophy and tubular loss
6. Other (changes not considered to be due to rejection)

of the renal compartments comprising interstitium (i), tubules (t), vessels (v) and glomeruli (g) as: 0=absent, 1=mild, 2=moderate and 3=severe (Table-2).

Banff 1997: In Banff '97[8] the significant change was that for the specimen to be adequate, it needed two cortical cores, sections thickness of 3-4µm, which had 10 or more glomeruli with at least two arteries bigger than arterioles.

Category 2, Hyper-acute rejection in the first Banff, was given renamed antibody-mediated rejection (AMR), with two subcategories of hyper-acute rejection, and accelerated acute rejection.

Category 4, Acute rejection in the first Banff, was substituted with acute/active rejection, and grades of acute rejection were changed to type/grade as: Type (Grade) I: (Tubulo-interstitial inflammation only), IA: Interstitial inflammation moderate-severe (i2, i3) and/or tubulitis moderate (t2), IB: Tubulitis severe (t3); Type (Grade) II: (Intimal arteritis), IIA: Intimal arteritis mild-moderate (v1), IIB: Intimal arteritis severe (v2); Type (Grade) III: Transmural arteritis and/or fibrinoid necrosis (v3).

Banff 2001: In 2003, the report of the Banff

Table-2: Numerical codes, specimen adequacy, and minimum sampling standards.[3]

Qualify diagnostic categories 3, 4, and 6 from Table 1 by g, i, t, v, and ah coding		
g	0, 1, 2, 3	no, mild, moderate, severe glomerulitis (g3 = mononuclear cells in capillaries of all or nearly all glomeruli with endothelial enlargement and luminal occlusion)
i	0, 1, 2, 3	no, mild, moderate, severe interstitial mononuclear cell infiltration (In rejection oedema and lymphocyte activation usually accompany mononuclear cell infiltration; i3 = > 50% of parenchyma inflamed)
t	0, 1, 2, 3	no, mild, moderate, severe tubulitis (t3 = > 10 mononuclear cells per tubule or per 10 tubular cells in several tubules)
v	0, 1, 2, 3	no, mild, moderate, severe intimal arteritis (v3 = severe intimal arteritis and/or transmural arteritis and/or haemorrhage and recent infarction)
ah	0, 1, 2, 3	no, mild, moderate, severe nodular hyaline afferent arteriolar thickening suggestive of cyclosporine toxicity (ah3 = severe PAS-positive thickening in many arterioles)
Qualify diagnostic category 5 from Table 1 by cg, ci, ct, and cv with different definitions		
cg	0, 1, 2, 3	no, mild, moderate, severe chronic transplant glomerulopathy
ci	0, 1, 2, 3	no, mild, moderate, severe interstitial fibrosis, often with mononuclear cell inflammation
ct	0, 1, 2, 3	no, mild, moderate, severe tubular atrophy and loss
cv	0, 1, 2, 3	no, mild, moderate, severe fibrous intimal thickening often with elastica fragmentation (cv3 indicates complete occlusion); (cg and cv lesions suggest the presence of chronic rejection)
Both acute and chronic codes can be used together if the situation warrants		
Specimen adequacy (state number of glomeruli in report)		
Unsatisfactory		No glomeruli or arteries
Marginal		1-6 glomeruli with artery
Adequate		7 or more glomeruli with artery
Minimum sampling :7 slides with 3 H & E, 3 PAS and 1 trichrome		

g: Glomerular, i: Interstitial, t: Tubular, v: Vascular, ah: Arteriolar hyalinosis, cg: Chronic glomerular, ci: Chronic interstitial, ct: Chronic tubular, cv: Chronic vascular.

2001 was published,[9] in which the peritubular capillaries (ptc) staining with split C4 complement component (C4d) was accepted as the marker AMR and classification of AMR was established thus: Type (Grade) I: C4d+, Acute tubular necrosis (ATN) like with minimal inflammation; Type (Grade) II: C4d+, capillary margination and/or thrombosis; Type (Grade) III: C4d+, transmural arteritis (v3).

The previous category of acute/active rejection was renamed acute/active cellular rejection.

Banff 2005: The report of the 8th Banff Conference, which took place in July 2005, was published in 2007.[11] The major amendments were switch of classification as per its pathophysiological basis, namely antibody-mediated rejection (ABMR) and T-cell-mediated rejection (TCMR), either of which could be acute or chronic; instead of acute on chronic. This classification deleted CAN, and re-classified the following categories:

Category 2: ABMR:

(i) Acute ABMR: (acute humoral rejection):

Acute ABMR occurs due to anti-donor antibodies and can occur on the operating table, or may take weeks to months. The microscopic features include ATN, presence of neutrophils in the ptc, thrombi and fibrinoid necrosis, along with C4d deposition.[18]

(ii) Chronic ABMR: (chronic humoral rejection)

This is suggested if there is interstitial fibrosis and tubular atrophy associated with glomerular, capillary and arteriolar pathology with deposition of C4d in ptc and/or glomeruli, associated with the presence of donor-specific antibodies.[19]

Category 4: TCMR:

(i) Acute TCMR: It occurs after 5-6 days, characterised by interstitial infiltrate of mononuclear cells with interstitial oedema, tubulitis, endarteritis, and rarely transplant glomerulitis.

(ii) Chronic active TCMR: It is characterised by arterial intimal fibrosis with mononuclear cell infiltration, and formation of neo-intima.

Category 5: CAN was replaced by the term Interstitial fibrosis and tubular atrophy.

Banff 2007, 2009 and 2011: The key change in Banff '07 was the addition of C4d staining.[12] The ptc C4d staining was graded as C4d0 = negative, C4d1- minimal 1-10%, C4d2 = focal 10-50%, and C4d3 = diffuse >50%.

In Banff '09, the only change from Banff '07 classification was that the presence of ATN which was described as indeterminate for 'C4d deposition without morphologic evidence of active rejection'.[13] Banff 2011 added C4d-negative ABMR.[14]

Banff 2013 and 2015: The 12th Banff Conference took place in Comandatuba, Brazil, from August 19 to 23, 2013. The key result of the conference was describing the criteria for the diagnosis of C4d-negative ABMR and the modification of classification accordingly.[15]

Revised (Banff 2013) classification of ABMR in renal allografts were:

Acute/active ABMR: The three features that must be present for diagnosis are:

1. Histologic evidence of acute tissue injury, including one or more of the following:

- Microvascular inflammation (g>03 and/or peritubular capillaritis [ptc]>0).

- Intimal or transmural arteritis (v>0).

- Acute thrombotic microangiopathy in the absence of any other cause.

- Acute tubular injury in the absence of any other apparent cause.

2. Evidence of current/recent antibody interaction with vascular endothelium, including at least one of the following:

- Linear C4d staining in ptc (C4d2 or C4d3 by interstitial fibrosis [IF] on frozen sections, or C4d>0 by immunohistochemistry [IHC] on paraffin sections).

- At least moderate microvascular inflammation ([g + ptc] > 2).

- Increased expression of gene transcripts in the biopsy tissue indicative of endothelial injury if thoroughly validated.

3. Serological evidence of donor-specific antibodies (DSAs) (human leukocyte antigen [HLA] or other antigens).

Chronic, active ABMR: The three features that must be present for diagnosis are:

1. Morphological evidence of chronic tissue injury, including one or more of the following:

- Transplant glomerulopathy (TG) (chronic glomerular [cg]>0) if no evidence of chronic thrombotic microangiopathy.

- Severe ptc basement membrane multilayering (requires electron microscopy [EM]).

- Arterial intimal fibrosis of new onset excluding other causes.

2. Evidence of current/recent antibody interaction with vascular endothelium, including at least one of the following:

- Linear C4d staining in ptc (C4d2 or C4d3 by IF on frozen sections, or C4d>0 by IHC on paraffin sections).

- At least moderate microvascular inflammation ([g + ptc] > 2).

- Increased expression of gene transcripts in the biopsy tissue indicative of endothelial injury if thoroughly validated.

3. Serological evidence of DSAs (HLA or other antigens).

C4d staining without evidence of rejection: The three features that all must be present for diagnosis are:

1. Linear C4d staining in ptc (C4d2 or C4d3 by IF on frozen sections, or C4d>0 by IHC on paraffin sections).

2. g = 0, ptc = 0, cg = 0 by light microscopy and by EM if available, v = 0; no thrombotic microangiopathy (TMA), no ptc basement membrane multi-layering, no acute tubular injury in the absence of any other apparent cause for this.

3. No acute cell-mediated rejection (Banff 97 type 1A or greater) or borderline changes.

Vancouver, Canada, hosted the 13th Banff meeting in 2015, which reviewed the clinical impact of updates of C4d-negative ABMR, thereby increasing the diagnostic accuracy of acute/active and chronic active ABMR in renal transplant biopsies.[16]

Banff 2017: The 2017 conference mainly concentrated on the clinical outcomes of inflammation in areas of interstitial fibrosis and tubular atrophy (i-IFTA) and its association with TCMR. It also focussed on the diagnosis of ABMR and the evolution of molecular diagnostics.[17]

Banff 2015 had for the first time described that the tubulointerstitial as well as the vascular compartment can show chronic active TCMR. It did not give any specific criteria that these tubulointerstitial changes would help in diagnosing chronic active TCMR. Inflammation involving more than a quarter of areas of cortex with IFTA, corresponding to Banff 2015 i-IFTA scores 2 and 3, were associated with high risk of graft loss.[20-23] Therefore, in 2017, the conference revised the classification and added moderate i-IFTA plus moderate or severe tubulitis as diagnostic of chronic active TCMR, and it included the part played by augmented expression of gene transcripts/classifiers in the diagnosis of active ABMR.[17]

Banff 2019: The 15th conference was held from September 23 to 27, 2019, in the US, and refined the criteria for chronic active (CA) TCMR, borderline, and ABMR. Agreement of the diagnosis of borderline (suspicious) for acute TCMR was also achieved.[5]

Banff '19 for clarity recommends that tubulitis can be independently scored, excluding severely atrophic tubules, both in areas of preserved cortex (Banff t score) and within (Banff t-IFTA score) areas of cortical IFTA (Table-3).

Longitudinal studies[24] showed no effect of isolated t lesions on graft outcomes, consensus was also achieved for the diagnosis of borderline acute TCMR which read as follows: "interstitial inflammation involving 10%-25% of non-sclerotic cortex (Banff i1) with at least mild tubulitis (t>0)." The minimum lesion for a borderline diagnosis is thus i1t1.

The main drawback of this classification is that it sub-classifies ABMR into only active or CA and chronic inactive subtypes, but it did not demonstrate "the different morphological and molecular lesions at different post-transplant time points in antibody-mediated tissue injury".[25,26]

The majority favoured (chronic) active ABMR with (mild, moderate, severe) activity and (mild, moderate, severe) chronicity and included the Banff lesion scores in the text of the diagnostic line for the biopsy report or in a table. It was the choice of the pathologists whether they adopt these wordings, or they just write the Banff lesion score as specific (Table-4). Descriptions and ideal starting point for mild, moderate, and severe activity and chronicity still needed to be confirmed by more studies.

Table-3: Banff scores used in grading of acute and chronic active antibody-mediated rejection (ABMR) and T-cell-mediated rejection (TCMR).[4]

Acute Banff scores	Grading (0, 1, 2, 3)	Chronic Banff scores	Grading (0, 1, 2, 3)	Acute & chronic Banff scores	Grading (0, 1, 2, 3)
i		ci		ti	
t		ct		i-IFTA	
v		cv		t-IFTA	
g		cg			
ptc		ptcml			
C4d					

i: Inflammation, t: Tubulitis, v: Endarteritis (intimal arteritis), g: Glomerulitis, ptc: Peritubular capillaritis, ci: Interstitial fibrosis in cortex, ct: Tubular atrophy in cortex, cv: Arterial intimal fibrosis, Ptcml: Peritubular capillary basement membrane multilayering, ti: Total cortical inflammation, i-IFTA: Inflammation in scarred, t-IFTA Tubulitis in tubules within scarred cortex.

Table-4: Diagnostic categories for renal allograft rejection (2019 Banff Classification).[4]

Category 1: Normal biopsy or nonspecific changes

Category 2: Antibody-mediated changes

Active ABMR; all 3 criteria must be met for diagnosis

1. Histologic evidence of acute tissue injury, including 1 or more of the following:
   - Microvascular inflammation (g > 0 and/or ptc > 0), in the absence of recurrent or de novo glomerulonephritis, although in the presence of acute TCMR, borderline infiltrate, or infection, ptc ≥ 1 alone is not sufficient and g must be ≥ 1
   - Intimal or transmural arteritis (v > 0)
   - Acute thrombotic microangiopathy, in the absence of any other cause
   - Acute tubular injury, in the absence of any other apparent cause
2. Evidence of current/recent antibody interaction with vascular endothelium, including 1 or more of the following:
   - Linear C4d staining in peritubular capillaries or medullary vasa recta (C4d2 or C4d3 by IF on frozen sections, or C4d > 0 by IHC on paraffin sections)
   - At least moderate microvascular inflammation ([g + ptc] ≥2) in the absence of recurrent or de novo glomerulonephritis, although in the presence of acute TCMR, borderline infiltrate, or infection, ptc ≥ 2 alone is not sufficient and g must be ≥1
   - Increased expression of gene transcripts/classifiers in the biopsy tissue strongly associated with ABMR, if thoroughly validated
3. Serologic evidence of circulating donor-specific antibodies (DSA to HLA or other antigens). C4d staining or expression of validated transcripts/classifiers as noted above in criterion 2 may substitute for DSA; however thorough DSA testing, including testing for non-HLA antibodies if HLA antibody testing is negative, is strongly advised whenever criteria 1 and 2 are met

Chronic active ABMR; all 3 criteria must be met for diagnosis

1. Morphologic evidence of chronic tissue injury, including 1 or more of the following:
   - Transplant glomerulopathy (cg > 0) if no evidence of chronic TMA or chronic recurrent/de novo glomerulonephritis; includes changes evident by electron microscopy (EM) alone (cg1a)
   - Severe peritubular capillary basement membrane multilayering (ptcml1; requires EM)
   - Arterial intimal fibrosis of new onset, excluding other causes; leukocytes within the sclerotic intima favour chronic ABMR if there is no prior history of TCMR, but are not required
2. Identical to criterion 2 for active ABMR, above
3. Identical to criterion 3 for active ABMR, above, including strong recommendation for DSA testing whenever criteria 1 and 2 are met. **Biopsies meeting criterion 1 but not criterion 2 with current or prior evidence of DSA (post-transplant) may be stated as showing chronic ABMR, however remote DSA should not be considered for diagnosis of chronic active or active ABMR**

Chronic (inactive) ABMR

1. cg > 0 and/or severe ptcml (ptcml1)
2. Absence of criterion 2 of current/recent antibody interaction with the endothelium
3. Prior documented diagnosis of active or chronic active ABMR and/or documented prior evidence of DSA

C4d staining without evidence of rejection; all 4 features must be present for diagnosis

1. Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by IF on frozen sections, or C4d > 0 by IHC on paraffin sections)
2. Criterion 1 for active or chronic active ABMR not met
3. No molecular evidence for ABMR as in criterion 2 for active and chronic active ABMR
4. No acute or chronic active TCMR, or borderline changes

Category 3: Borderline (Suspicious) for acute TCMR

Foci of tubulitis (t1, t2, or t3) with mild interstitial inflammation (i1), or mild (t1) tubulitis with moderate-severe interstitial inflammation (i2 or i3)

No intimal or transmural arteritis (v = 0)

Category 4: TCMR

Acute TCMR

Grade IA: Interstitial inflammation involving >25% of non-sclerotic cortical parenchyma (i2 or i3) with moderate tubulitis (t2) involving 1 or more tubules, not including tubules that are severely atrophic

Grade IB: Interstitial inflammation involving >25% of non-sclerotic cortical parenchyma (i2 or i3) with severe tubulitis (t3) involving 1 or more tubules, not including tubules that are severely atrophic

Grade IIA: Mild to moderate intimal arteritis (v1), with or without interstitial inflammation and/or tubulitis

Grade IIB: Severe intimal arteritis (v2), with or without interstitial inflammation and/or tubulitis

Grade III: Transmural arteritis and/or arterial fibrinoid necrosis involving medial smooth muscle with accompanying mononuclear cell intimal arteritis (v3), with or without interstitial inflammation and/or tubulitis

Chronic active TCMR

Grade IA: Interstitial inflammation involving >25% of sclerotic cortical parenchyma (i-IFTA2 or i-IFTA3) AND > 25% of total cortical parenchyma (ti2 or ti3) with moderate tubulitis (t2 or t-IFTA2) involving 1 or more tubules, not including severely atrophic tubules; other known causes of i-IFTA should be ruled out

Grade IB: Interstitial inflammation involving >25% of sclerotic cortical parenchyma (i-IFTA2 or i-IFTA3) AND > 25% of total cortical parenchyma (ti2 or ti3) with severe tubulitis (t3 or **t-IFTA3**) involving 1 or more tubules, not including severely atrophic tubules; other known causes of i-IFTA should be ruled out

Grade II: Chronic allograft arteriopathy (arterial intimal fibrosis with mononuclear cell inflammation in fibrosis and formation of neointima). This may also be a manifestation of chronic active or chronic ABMR or mixed ABMR/TCMR

ABMR: Antibody mediated rejection, TCMR: T-cell mediated rejection, g: Glomerulitis, ptc: Peritubular capillaritis, TMA: Thrombotic microangiopathy, DSA: Donor-specific antibody, HLA: Human leukocyte antigen.

Future prospects: Although much has been done to improve the histological diagnose and to correlate it with clinical presentation,[27] there are still limitations and may issues still remain to be studied, and there is a need to develop additional diagnostic tools, including molecular diagnostics.[28,29] During the 2019 meeting, the discussion revolved not only around the future role of artificial intelligence (AI), machine learning (ML),[30] as well as deep learning (DL)[31-33] but it also included application in diagnosis and personalised medication in cases of organ transplantation. As these fields are very recent, they are not well understood by many clinicians and pathologists.

The 16th Banff meeting and the 30-year anniversary of the Banff Classification will be held where it all started' in Banff, Canada. It is now scheduled for September 19-23, 2022, and is likely to address these new themes using the ongoing Banff process of international consensus-building framework.

Conclusion

This perspective review concentrates on the work done in the last three decades on the standardized classification for renal allograft biopsy which began in Banff, Canada in 1991, with some hints to future prospects The Banff classification has undergone many reviews in light of new evidence and techniques and the next meeting will be held where it all started in Banff Canada in September 2022.

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