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MEETING REPORT

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The Banff 2017 Kidney Meeting Report: Revised diagnostic criteria for chronic active T cell–mediated rejection, antibody-mediated rejection, and prospects for integrative endpoints for next-generation clinical trials

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Abbreviations: AMBR, antibody-mediated rejection; BCAR, biopsy-confirmed acute rejection; cg, Banff chronic glomerulopathy score; DSA, donor-specific antibody; DSAST, "DSA-specific" transcript set; EMA, European Medicines Awgency; EM, electron microscopy; FDA, US Food and Drug Administration; FFPE, formalin-fixed paraffin-embedded; g, Banff glomerulitis score; IF, immunofluorescence; IFTA, interstitial fibrosis and tubular atrophy; i-IFTA, inflammation in areas of interstitial fibrosis and tubular atrophy; MVI, microvascular inflammation; ptc, Banff peritubular capillaritis score; PTCBML, peritubular capillary basement membrane multilayering; STAR, Sensitization in Transplantation: Assessment of Risk; TCMR, T cell–mediated rejection; TG transplant glomerulopathy

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The kidney sessions of the 2017 Banff Conference focused on 2 areas: clinical implications of inflammation in areas of interstitial fibrosis and tubular atrophy (i-IFTA) and its relationship to T cell–mediated rejection (TCMR), and the continued evolution of molecular diagnostics, particularly in the diagnosis of antibody-mediated rejection (ABMR). In confirmation of previous studies, it was independently demonstrated by 2 groups that i-IFTA is associated with reduced graft survival. Furthermore, these groups presented that i-IFTA, particularly when involving >25% of sclerotic cortex in association with tubulitis, is often a sequela of acute TCMR in association with underimmunosuppression. The classification was thus revised to include moderate i-IFTA plus moderate or severe tubulitis as diagnostic of chronic active TCMR. Other studies demonstrated that certain molecular classifiers improve diagnosis of ABMR beyond what is possible with histology, C4d, and detection of donor-specific antibodies (DSAs) and that both C4d and validated molecular assays can serve as potential alternatives and/or complements to DSAs in the diagnosis of ABMR. The Banff ABMR criteria are thus updated to include these alternatives. Finally, the present report paves the way for the Banff scheme to be part of an integrative approach for defining surrogate endpoints in next-generation clinical trials.

KEYWORDS
classification systems: Banff classification, kidney transplantation/nephrology, molecular biology, pathology/histopathology, rejection, translational research/science

1 | INTRODUCTION

The XIV Banff Conference for Allograft Pathology was held March 27-31, 2017, in Barcelona, Spain, in conjunction with the annual meeting of the Catalan Society of Transplantation. A total of 479 delegates from 23 countries attended the conference, including pathologists, immunologists, physicians, surgeons, and immunogeneticists. The main aim of the 2017 conference was to revisit the current diagnostic criteria for chronic T cell–mediated rejection (TCMR), especially the significance of inflammation in areas of interstitial fibrosis and tubular atrophy (i-IFTA). In addition, discussion related to the relevance and potential integration of molecular transplant diagnostics into the Banff classification was continued along the roadmap developed at the 2015 Banff meeting.[1] This included an update of the criteria for assessing molecular features related to antibody-mediated tissue injury as a potential alternative/complement to donor-specific antibodies (DSAs) for diagnosing antibody-mediated rejection (ABMR). In alignment with ongoing efforts of the American Society of Transplantation (Transplant Therapeutics Consortium) and the American Society of Histocompatibility and Immunogenetics (STAR initiative [Sensitization in Transplantation: Assessment of Risk]), the Banff 2017 conference was preceded by a full-day premeeting on "New Endpoints for Next-Generation Clinical Trials" in which the current and future role of the Banff classification and unmet needs for the field with regard to surrogate endpoints were discussed. In addition, the meeting included as a standing item an update session on the ongoing activities of the Banff Working Groups, which is summarized in Table 1.

This meeting report focuses on the main outcomes from the Banff kidney sessions, and the resulting changes to the classification. The main conclusions from the 2017 Banff liver, heart, lung, pancreas, and vascularized composite allograft sessions will be published elsewhere. The next XV Banff meeting will be held jointly with the American Society of Histocompatibility and Immunogenetics in Pittsburgh, PA, September 23-27, 2019.

2 | DEFINING ENDPOINTS IN KIDNEY TRANSPLANTATION FOR NEXT-GENERATION CLINICAL TRIALS: PLACE OF THE BANFF SCHEME AND COMBINED ENDPOINTS

The approval of novel drugs in the field of kidney transplantation has been dampened by several factors. One of the explanations for the failure of trials testing new agents has been the success of the "gold standard" immunosuppression demonstrated in the Symphony study and on the other hand, the relative lack of success of new agents.[2] The US Food and Drug Administration (FDA)/European Medicines Agency (EMA)-approved primary endpoints, such as 1-year graft and patient survivals, are irrelevant today for superiority trials, due to excellent graft and patient survival in the overall transplant populations (~95%) and are difficult to improve further. Designing studies with 5- or 10-year graft and patient survival as primary endpoints are unrealistic in terms of costs, especially as transplantation is a small field/market

with potentially repositionable drugs known already for their adverse reaction profiles. Acute rejection is also recognized as a primary endpoint for clinical trials in transplantation by health authorities, but TCMR and ABMR do not have the same impact on graft outcome. Furthermore, the transplant community and the industry aiming to introduce new agents are addressing these issues independently.

The Banff process has evolved from being a primarily pathology-driven group to a more comprehensive and multidisciplinary approach that includes relevant subject matter expertise from immunogeneticists, clinicians, and pathologists with the goal to establish and refine integrative diagnostic standards in transplantation. To accelerate the development of new immunosuppressive agents, Banff is currently working closely with regulatory agencies and international societies to define realistic and feasible endpoints and approaches for next-generation clinical trials.[3,4] Various specialty societies and consortia have identified the unmet need for the validation of surrogate endpoints in order to evaluate responses to therapy and predict long-term kidney allograft outcomes. During the 2017 Banff premeeting, those new challenges were addressed with a specific focus on histologic, immunologic, and molecular endpoints.

2.1 | Histopathology as an endpoint

Rejection episodes confirmed by histology are recognized as the cornerstone of diagnosis and prognosis in kidney and transplantation pathology. However, the current FDA/EMA-approved surrogate histologic endpoint, biopsy-confirmed acute rejection (BCAR), is no longer reflecting current diagnostics in renal transplantation, where the impact of acute TCMR on outcome has declined. As an example, in the BENEFIT Study, BCAR was used as primary endpoint for non-inferiority, and there was more BCAR (TCMR) in the arm receiving belatacept (vs cyclosporine), but this did not lead to a higher rate of graft loss in the long term as shown by the BENEFIT-EXT study.[5,6] To regain usefulness as primary endpoints for trials in kidney transplantation, histologic markers need to follow a validation process as outlined during the Banff meeting (Table 2A).

2.2 | Intragraft gene expression as an endpoint

In Table 2B, we listed our recommendations on best practices for molecular endpoints in clinical trials. Potential diagnostic and prognostic molecular endpoints and biomarkers are listed in Tables 3 and 4.

2.3 | Anti-HLA DSAs as an endpoint

To be a potential surrogate endpoint, anti-HLA DSAs have not only to be considered within the context of their potential limitations (titration rather than mean fluorescence intensity to reveal oversaturation) but also by integrating their properties (eg, complement activating capacity, IgG subclasses, cytotoxic effect). However, current shortcomings of DSA testing (variability in test methods, diagnostic threshold definitions, clinical significance standards) are known to limit its utility as a sole endpoint. Ongoing efforts of the STAR initiative are aiming to address these.

2.4 | Potential of innovative combined endpoints

The participants in the 2017 Banff premeeting support a path toward integrated diagnostic and prognostication systems by exploring opportunities provided by advanced data and applied statistics from the field of machine learning.[7] To this end, the Banff group formed a new working group on surrogate endpoints aimed at fostering collaboration with other professional societies and regulatory agencies on the common goal to develop a path forward to successful next-generation multicenter trials and approval of novel drugs in solid organ transplantation.

3 | 2017 REVISIONS TO THE BANFF CLASSIFICATION

3.1 | T cell–mediated rejection

The Banff 2015 meeting report noted for the first time that chronic active TCMR may be manifest in the tubulointerstitial as well as in the vascular compartment.[1] However, the current Banff classification does not provide specific criteria regarding how tubulointerstitial changes should be considered for diagnosing chronic active TCMR, although Banff consensus criteria for semiquantitatively scoring inflammation in areas of IFTA (i-IFTA) as a histologic lesion have been established. Although potential problems in scoring i-IFTA might be anticipated as scattered inflammatory cells are often seen in what might be considered by many pathologists to be bland fibrosis, the Paris group[8] reported good agreement among 3 pathologists in grading i-IFTA according to the Banff 2015 criteria, with complete agreement between all 3 pathologists in 101 (67%) of 150 cases, and a κ value of .62.

The impact of i-IFTA on graft outcomes was first suggested by the finding of Mengel et al[9] that total cortical inflammation (Banff ti score) was more predictive of graft loss than inflammation in nonsclerotic areas of cortex (Banff i score). Independently, the DeKAF study[10] showed a strong association between the severity of i-IFTA and graft loss, far stronger than that of IFTA alone. Degrees of inflammation involving >25% of areas of cortex with IFTA (corresponding to Banff 2015 i-IFTA scores 2 and 3) were significantly associated with an increased risk of graft loss in multivariate models.[10] These findings were independently validated by recent studies of Lefaucheur, Loupy, and coworkers[8] and Nankivell et al[11] The amenability of i-IFTA to immunosuppressive therapy remains an important question, and findings of the DeKAF study showed that the effect of i-IFTA on graft survival was not significantly affected by treatment for concomitant acute TCMR.[10] Still, data presented by the Paris group[8] showed that i-IFTA is related to underimmunosuppression, and both this group and Nankivell et al[11] found that i-IFTA is typically preceded by TCMR. Furthermore, the frequency of i-IFTA in protocol biopsy specimens has declined in the era of tacrolimus-based immunosuppression compared with that of cyclosporine-based immunosuppression.[11] Taken together, these findings suggest that i-IFTA, at least in many instances, is related to chronic underimmunosuppression and thus can represent

TABLE 1 Update on active Banff working groups

	Leaders	Issues to address	Group progress/future plans
TCMR	V. Nickeleit, P. Randhawa	Possible incorporation of i-IFTA into classification; possible elimination of borderline category; reevaluate thresholds for i and t and possible addition of other findings (eg, edema) to TCMR diagnostic criteria.	To this point compiled 81 cases of "pure" TCMR with complete clinical/pathologic data sets, and an additional 140 cases with incomplete data. More cases of "pure" TCMR with complete pathologic and clinical data for evidence-based analysis of TCMR/borderline thresholds are required; these cases need to have documented absence of DSA and sufficient follow-up. Survey among renal pathologists (including very experienced) revealed nonuniform application of current Banff TCMR cutoffs, consideration of non-Banff lesions in TCMR diagnosis, grading or nongrading of i-IFTA. See also discussion of i-IFTA scoring and clinical relevance for diagnosis of chronic active TCMR.
Sensitized	L. Cornell, E. Kraus, S. Bagnasco, C. Schinstock, D. Dadhania	Define criteria for highly sensitized patients (HS), determine consensus for what personnel and facilities are needed for centers to perform transplantation in HS recipients, standardize the definitions related to management of sensitized transplant recipients. Evaluate current practices of centers performing renal transplants in sensitized recipients. Evaluate how clinicians interpret and apply Banff nomenclature, and recommend changes to wording of classification to optimize the use of Banff data in patient care.	Survey regarding clinical practice related to highly sensitized patients indicates that: • Clinicians often fail to recognize chronic elements of ABMR (eg, cg >0) • Clinicians more likely to consider a diagnosis of chronic, active ABMR if C4d is negative, even if there is no TG, PTCBML, or IFTA • The term "acute" (in acute/active ABMR) is confusing to clinicians, and consequently it has been removed from the Banff classification—see Table 5 • Further improve communication between pathologists and clinicians regarding reporting of biopsy findings in HS, including the presence of C4d-negative early ABMR
Molecular	M. Mengel, B. Sis	Develop consensus guidelines for: Circumstances under which it is advisable to apply molecular analysis to renal biopsy tissue and/or serum/urine collected at the time of biopsy—also see Tables 4 and 6 Standardize diagnostic criteria and procedures for a gene expression analysis approaches in renal transplantation.	Further data from experiences with gene expression analysis applied to FFPE tissue was presented: • the method can reproducibly be applied to almost any FFPE sample in different species • multicenter studies are under way or planned for applications in kidney, heart, pancreas, and lung transplantations
Electron microscopy	C. Roufosse, H.K. Singh	Interobserver variability and clinical correlations in cg1a lesions and PTCBML scoring. Potential refinement of PTCBML scoring criteria. Criteria for amount of GBM duplication and immune complex-type deposits allowable in cg1a. Multicenter study of the natural history, associations and predictive value of cg1a and PTCBML using consensus criteria. Define possible lower levels of PTCBML and endothelial cell changes that represent earlier and possibly reversible levels of injury (compared wih level of PTCBML required to diagnose chronic active ABMR in Banff 2013).	A survey showed that current Banff guidelines do not provide enough detail regarding when to do EM, and that current guidelines are often not followed due to cost restrictions or limited access to EM Future studies will focus on: • How reversible is cg1a? • What is the prognostic significance of cg1a compared with that of overt TG? • Is there a level of PTCBML, lower than that required to diagnose chronic active ABMR in Banff 2013, that is useful in the diagnosis of early chronic ABMR, and, if so, is this potentially reversible with treatment for ABMR? Goals: • To create a comprehensive teaching module for TG and PTCBML evaluation and guidelines for diagnosis of ultrastructural changes with a follow-up test using digital images • Multicenter validation of diagnostic criteria and final recommendations

(Continues)

TABLE 1 (Continued)

	Leaders	Issues to address	Group progress/future plans
Thrombotic microangiopathy (TMA)	M. Afrouzian, J. U. Becker, H. Liapis, S. Seshan	Establish uniform diagnostic criteria for TMA. Determine the frequency with which TMA occurs in renal allograft biopsy specimens. Determine if there are specific features of TMA in renal allografts that help resolve the differential diagnosis of the TMA when the cause is not readily apparent from clinical history, DSA/C4d, etc.	Survey of 26 centers showed TMA diagnosed in 5%-10% of biopsy specimens in 42% of centers, <5% in 35%, 10%-20% in 23% of centers. Focus future efforts on working with other groups (eg, KDIGO, ERKnet) in defining TMA uniformly in native and transplanted kidneys. Compare and contrast features of TMA in known cases of CNI-related TMA (from native kidneys of recipients of other solid organs), TMA in the setting of well-documented ABMR (DSA^+, $C4d^+$), and recurrent aHUS to assess differences in morphologic and other (eg, laboratory, molecular) features between these that will be potentially useful in determining the most likely etiology in TMA cases where the latter is not clear.
Recurrent glomerular disease	N. Alachkar, S. Bagnasco	Establish pathologic guidelines for early recurrence of glomerular diseases, including FSGS, IgA nephropathy, and MPGN/C3GN. What are frequencies, clinical manifestations, and pathologic characteristics of recurrent/de novo glomerular disease? Can any of these predict recurrence and/or graft outcomes? Understand the pathologic changes of recurrent glomerular diseases occurring concurrently with rejection and other transplant-associated lesions.	Biopsy specimens are now collected from 5 centers and preliminary studies confirm IgA nephropathy and FSGS as the most prevalent recurring diseases. Future directions: Are there clinical and/or pathologic features of the *native* disease that predict likelihood of recurrence? Are there clinical and/or pathologic features of the *recurrent* disease in the allograft that predict graft loss? Which pathologic analyses (IF, EM, others) are needed for optimal and early diagnosis of recurrent disease? Is the apparent association of recurrent glomerular disease with acute rejection related to biopsy bias (ie incidental discovery of recurrent disease in biopsies done to r/o rejection), under-immunosuppression, or both?
Surrogate endpoints (new working group)	A. Loupy, B. Orandi	Respond to the unmet need raised by the FDA meeting held in Arlington in 2015: build a validated multicenter composite scoring system integrating histopathology with other relevant allograft biomarkers to predict long-term allograft outcome.	*See summary of Banff pre-meeting "New Endpoints for Next Generation Clinical Trials"*
HIV^+/HIV^+ renal transplants (new working group)	S. Bagnasco	Are there specific issues/difficulties in diagnosing transplant-associated pathologic lesions (TCMR, ABMR, others and components of these) in the setting of concurrent HIV-associated pathology (related to the virus itself and to anti-retroviral therapy). Do the incidence, pathology, and therapeutic response of rejection in cases of HIV+/HIV+ renal transplantation differ from those with HIV- donor kidneys transplanted into HIV- recipients and into HIV+ recipients. If so, how are these differences manifest? Overall, develop a set of evidence-based guidelines for HIV+/HIV+ renal transplants.	Efforts are underway to standardize the histological assessment of HIV-associated nephropathies in native kidneys (eg, KDIGO). Any scoring of such lesions in transplants should follow the native kidney criteria. Subsequently transplant specific pathologies can be defined. Further efforts of this BWG will focus on working with the native kidney groups on standardizing the HIV-related pathology scoring.
Banff rules and dissimination (new working group)	J. U. Becker, C. Roufosse	Collation of contents of previous Banff reports in a central web-based, updatable repository including diagnostic parameters, definitions and rules. Elaboration of a minimum dataset and algorithms for application of Banff classification.	Finalisation of the collation of current content during a meeting in London, UK in September 2017. Preparation of a review manuscript with contents of previous Banff reports up to 2015. Incorporation of possible changes in Banff 2017 report to content for the web-based repository in 2018.

chronic active TCMR. Inflammation in non-IFTA and IFTA areas can coexist in the same biopsy specimen. Such biopsy specimens should still be diagnosed as chronic active TCMR and not labeled acute plus chronic active TCMR, because the latter already addresses the acute/active component in the rejection process. In other words, a biopsy fulfilling the diagnostic criteria for chronic active TCMR should not be given a second diagnosis of Borderline or acute TCMR. However, biopsies with chronic active TCMR can have an additional diagnosis of ABMR. In general, i-IFTA likely reflects a response to wounding of injured nephrons and renal tissue, as shown by molecular studies showing that any progressing chronic kidney diseases are associated with increased expression of acute kidney injury transcripts. Thus, i-IFTA is the morphologic correlate of active injury, compared with IFTA with no inflammation, and predicts disease progression as part of an active injury process damaging the nephron and potentially warranting treatment.[12,13]

Clearly, i-IFTA is not a specific lesion, and adding i-IFTA by itself, even if moderate to severe, to the classification as diagnostic of chronic active TCMR does not appear warranted based on present data. It is well known that many other disease processes, including BK virus infection, pyelonephritis, ABMR, recurrent glomerulonephritis, and obstruction, may at some point present with i-IFTA. The nonspecificity of i-IFTA for rejection, proved by the fact that it occurs in native kidneys, was the main reason why i-IFTA and tubulitis in atrophic tubules was specifically excluded from the classification at the first Banff meeting. However, since 1991, immunosuppression has changed and graft survival improved with more patients presenting late posttransplantation with i-IFTA requiring differential diagnostic resolution to guide treatment. Based on the most recent data taking this evolution into account, i-IFTA is likely to be a manifestation of TCMR when associated with other features of ongoing T cell–mediated alloimmunity, such as tubulitis or a history of TCMR episodes in a patient, especially after excluding other diseases known to be associated with i-IFTA (eg, BK, ABMR, GN, obstruction). The study from the Paris group did show that i-IFTA was significantly correlated with the presence of tubulitis, in both scarred and nonscarred areas of the cortex.[8] Thus, at present and to minimize overdiagnosis, tubulointerstitial lesions of chronic active TCMR have been added to the working classification (Table 5) as a combination of i-IFTA and tubulitis involving all but severely atrophic tubules, with moderately high thresholds for both (i-IFTA2-3; t2-3), a requirement for inflammation involving >25% of the total cortex present, and other differential diagnoses known to be associated with i-IFTA (eg, chronic pyelonephritis, BK nephropathy) being ruled out. Notably, Lefaucheur et al[8] found that i-IFTA scores of 2 and 3, but not 1, as well as t2 and t3 tubulitis (but not t1) within areas of IFTA, excluding severely atrophic tubules, were associated with an increased rate of graft loss. This conservative approach has served the Banff group well in the past, with the introduction of C4d-negative ABMR.[14] As with the latter (see later), future modifications will be considered as new data emerge from the Banff TCMR working group[1] as well as from other, independent investigators. Key issues here concern the threshold values of individual histologic lesions needed to diagnose chronic active TCMR, whether the Banff i-IFTA score or ti score is more predictive of graft outcomes, association with nonadherence and underimmunosuppression, and possibly response to newer immunosuppressive therapy. Response to increase immunosuppressive therapies should be studied, as well as whether molecular parameters associated with TCMR[15,16] may be useful in diagnosis.

TABLE 2 Banff recommendations on best practice for pathology and molecular endpoints in clinical trials

A. Banff recommendations on best practices for pathology endpoints in clinical trials
Pathologists to participate in the design and choice of endpoints
Panel of pathologists (3 optimal to avoid a tie)
Adjudication mechanism (how discordance between pathologists is addressed)
Whole slide digital images for centralized slide review
Auditable assessments (scoring that can be reviewed and audited externally)
Granular scoring (detailed phenotyping and lesions scoring considered for end-points)
Quantitate changes (use of continuous scores and percentages rather than semi-quantitative scoring)
Centralized processing of ancillary testing, eg IHC stains
B. Banff recommendations on best practices for molecular endpoints in clinical trials
The primary effort should be on applying molecular studies to biopsies
Large Reference data sets should be well annotated
High reproducibility/replication of assays
Pathogenesis based transcript strategy appears useful and can be completed by classifier approaches (no single gene test is specific)
Centralized testing advantageous for multi-center trials molecular analysis
Proper methodological approaches are needed (for both assay performance and data analysis, ...) Adds statistical power, potentially reducing sample size and costs
Quality Assurance is mandatory (inter-laboratory, inter-platform and inter-assay reproducibility; development of standardized positive and negative controls and quantitative diagnostic reference standard)

At this point, there is no borderline or suspicious category for chronic active TCMR, particularly as this category within acute TCMR has proved to be troublesome for treating clinicians and even for pathologists to define (see Tables 3 and 4 of ref. 1). Furthermore, low levels of i-IFTA (i-IFTA 1) and mild tubulitis within foci of IFTA were not correlated with graft survival in the study of Lefaucheur et al.[8]

Figure 1 depicts lesions of chronic active TCMR grades IA (panels A and B) and IB (panels C and D). Both show extensive i-IFTA, with the main difference being the extent of tubulitis, being moderate (t2) in grade IA and severe (t3) in grade IB. Interstitial edema is present as well, although the latter is not a requirement for i-IFTA and the inflammation may be present in areas of denser, more-evolved fibrosis as is shown in Figure 2, which depicts 3 other biopsy specimens showing i-IFTA with varying densities of interstitial fibrosis and degrees of interstitial

TABLE 3 Prime gene list of published studies in kidney transplantation and related diagnoses. Courtesy by Dr. Robert Colvin (Massachusetts General Hospital) and Dr. Alexandre Loupy (Paris Translational Research Center for Organ Transplantation INSERM U970)

ABMR	TCMR		TCMR	eGFR later	Exhaustion	Tolerance (Blood)	GoCAR	Glomerulus	TCMR	Constant rej	IFI27	ABMR	DSAT	TCMR		ENG	RHOJ
Adam	Sellares			Vitalone	Wherry	Rebolo-Mesa	O'Connell		Halloran	NIH	IGF	Halloran	Halloran	Venner		ERG	ROBO4
CAV1	ADAMDEC1	IFNG	BCL2	CITED4	CD244/2B4	ATXN3	ASB15	APOL1	ADAMDEC1	ADAM8	IL10	APOBEC3A	CDH13	ADAMDEC1	PSME2	EVA1C	S1PR1
CD34	AIM2	IL12RB1	CD4	EDA	BCL6	BCL2A1	CHCHD10	COL4A3	ANKRD22	ANP	IL1R	C21orf63	CDH5	AIM2	PSTPIP1	FCGR3A	S1PR5
CD74	ANKRD22	IL18BP	CXCL10	SLC19A3	BTLA	EEF1A1	FJX1	COL4A4	BTLA	BASP1	IL2RA	CAV1	COL13A1	ANKRD22	PTPN7	FGFBP2	SDR16C5
CDH13	AOAH	IL21R	CXCL9	SLC22A2	CD57	GEMIN7	KAAG1	COL4A5	CD28	Beta-2M	IL2RB	CCL4	CX3CR1	AOAH	RARRES3	GNG11	SELP
CDH5	APOL2	LAG3	GZMB	SLC25A15	CTLA4	IGLC1	KLH13	EHD3	CD72	CASP1	IL10RA	CDH13	DARC	APOL2	SH2D1A	GNLY	SH2D1B
CX3CR1	BTLA	LAIR1	IL1RL1	SLC4A1	EOMES	MS4A4A	MET	NPHS1	CD8A	CASP3	IL8	CDH5	FGFBP2	BTLA	SIRPG	HEG1	SOX7
CXCL11	CD274	LAP3	IL4	TMEM178	GATA3	NFKBIA	RNF149	NPHS2	CD96	CASP4	INDO	CETP	GNG11	CD274	SLA	HSPA12B	TEK
DARC	CD28	LCP2	WARS	TRAF4	IKZF2	RAB40C	RXRA	Misc	CXCL13	Cathepsin-S	INFG	CRHBP	GNLY	CD28	SLAMF8	HYAL2	TFF3
FGFBP2	CD3D	MYB			IL10	TNFAIP3	SERINC5	AICDA	IFNG	CCL-2	IP-30	CX3CR1	HLA-DRB3	CD3D	SP140	ICAM2	THBD
GATA3	CD72	PHEX	Macrophages	AKI	IL21		SPRY4	AIRE	IKZF3	CCL18	ISG20	CXCL10	ICAM2	CD72	ST8SIA4	IER5	TM4SF1
GNLY	CD84	PSME2	ARG1	Einecke	LAG3	TOLS	ST5	CCL5	IL12RB1	CCL19	JAK1	CXCL11	KLRF1	CD84	TAP1	IFI27	TM4SF18
IFNG	CD86	PSTPIP1	CD163	CPA3	NFAT	Colvin	TGIF1	CCR4	IL21R	CCL5	JAK2	DARC	MALL	CD86	TIGIT	IL18RAP	TRDV3
KLF4	CD8A	PTPN7	CD206	CTSS	PD1	BDCA2	WNT9A	CCR5	LAG3	CCR5	L-selectin	ECSCR	MYBL1	CD8A	TNFSF8	KLF2	VEGFC
KLRF1	CD8B	RARRES3	CD68	FCGR3A	PDL1/CD274	CCL21		CLEC4C	MIR155HG	CD14	LyGDI	FGFBP2	PGM5	CD8B	ABMR	KLRF1	VWF
MALL	CD96	SH2D1A	LGALS3	HAVCR1	PDL2	CD197/CCR7	CADI Progression	IL17	OR2I1P	CD2	MMP-9	GNG11	PLA1A	CD96	Venner	LAYN	
MYBL1	CTLA4	SIRPG	VEGFA	ITGB6	PRDM1	EPO	Menon JCI	IL2	PDCD1LG1	CRACC	Perforin	GNG11	PLAT	CTLA4	ACVRL1	LDLR	
PALMD	CXCR6	SLA		LCN2	TBX21	FOXP3	SHROOM3	MIF	PLA2G2D	CTLA-4	Plscramblase	GNLY	ROBO4	CXCR6	AGR2	LHX6	
PECAM1	DUSP2	SLAMF8	Plasma cells	LTF	TGFB1	IDO	COL1A1	MS4A1	PTPN7	CXCL10	PSMB10	KLF4	SH2D1B	DUSP2	AGR3	LST1	
PLA1A	EZH2	SP140	PRDM1	MEGF11	TIGIT	IFNA1		TNFRSF18/GITR	SCML4	CXCL11	PSMB8	MEOX1	SOX7	EZH2	ANXA1	MALL	
PLAT	FAM26F	ST8SIA4	IGHG1	NFKBIZ	TIM3	ITGAX/CD11C	Matrix		SH2D1A	CXCL9	PSMB9	PALMD	TEK	FAM26F	APOBEC3A	MCAM	
PSMB10	FCGR1B	TAP1	IGHG2	NNMT		LTA	COL1A1	Virus	SIRPB2	CXCR3	PSME1	PGM5	TM4SF18	FCGR1B	CAV1	MEOX1	
RHOJ	FGD2	TIGIT	IGHG3	OSMR	AMR	NOS2	COL3A1	BK large T Ag	SLA	CXCR4	STAT1	PLA1A		FGD2	CCL3	MMRN2	
ROBO4	GBP5	TNFSF8	IGHG4	RARRES1	Roufosse	PDPN	COL4A1	BK VP1	SLAMF8	FcGRI	TANK	RAMP3		GBP5	CD160	MYBL1	
RPS6	GIMAP5		IGHM	SOD2	VWF	TNFRSF3	COL5A1	CMV UL83	SP140	FNGR1	TAP1	RAPGEF5		GIMAP5	CD55	NOS3	
RPS6KB1	ICOS	CRM	IGHA1	SPLI	CDH5	TNFSF3	FN1	EBV LMP2	THEMIS	GBP1	Tapasin	ROBO4		ICOS	CD59	NPDC1	
SELE	IFI30	Sarwal	IGKC	VCAN	SOX7			Housekeeping	TIGIT	GBP2	TGF-B1	SOST		IFI30	CDH13	PALMD	
SH2D1B		BASP1	IGLC1	VMP1	PECAM1		Mast cells	Nanostring	TNFSF8	GBP4	TIMP1	SOX7		IFNG	CDH5	PECAM1	
SOX7	Eculiz Resp	CD6			DARC		Mengel	DDX50	TOX2	GZMA	TLR8	TM4SF18		IL12RB1	CFLAR	PGM5	
TBX21	Lefaucheur	CD7	RUNX3		SH2D1B		CPA3	GUSB	TRIM	HLA-A	TNF	TRD		IL18BP	COL13A1	PLA1A	
TEK	CCL4	CXCL10	TAP1		CX3CR1		TPSAB1	HDAC3		HLA-E	TNFSF10	VWF		IL21R	CRIP2	PLK2	
THBD	FCGR3A	CXCL9			GNLY		FCER1A	OAZ1		HLA-F	Ubiquitin			LAG3	CX3CL1	PPM1F	
TNF	MS4A7	INPP5D			MYBL			POLR2A		HLA-G	VCAM1			LAIR1	DARC	RAMP3	
TRIB1	MS4A6A	NKG7			FGFBP2			SDHA		HSPA1A	VIP			LAP3	ECSCR	RAPGEF5	
VWF	CXCL11	PSMB9			KLRF1			UBB		IFI17	WARS			LCP2	ELTD1	RASIP1	
											WSX1			MIR155	EMP3	RASSF9	

inflammation, edema, and tubulitis using 3 different histologic stains (hematoxylin and eosin, periodic acid–Schiff, and Masson trichrome). The silver-stained sections in Figure 1 show tubulitis in mildly to moderately atrophic tubules (best evident in panels B and D), and both of these biopsy specimens also show some severely atrophic tubules. The latter tubules are defined by having a diameter <25% of that of unaffected or minimally affected tubules on the biopsy, often with an undifferentiated-appearing, cuboidal, or flattened epithelium (or, in some cases, even loss of epithelium with denudation of the tubular basement membrane) and pronounced wrinkling and/or thickening of the tubular basement membrane. This definition of severely atrophic tubules also includes very small, endocrine-like tubules with very narrow lumens, although the basement membranes of the latter may not be thickened. Frequently, severely atrophic tubules will show tubulitis even if there is minimal accompanying interstitial inflammation; this is true even in native kidney biopsy specimens. Therefore, tubulitis in these tubules is presently not considered toward the diagnosis of chronic active TCMR (Table 5), although this point requires further study, which will be done by the TCMR working group. The interobserver reproducibility of pathologists to distinguish severely atrophic tubules from less atrophic ones will also need further testing, although encouraging results were reported by the Paris group.[8] They reported a complete agreement rate between 3 pathologists of 72% and a κ value of .58 in grading tubulitis in areas of IFTA excluding severely atrophic tubules, although the latter were not defined by a specific reduction in size.

3.2 | Antibody-mediated rejection

Several potential updates to the Banff 2015 criteria for ABMR were considered. The most important of these concerned potential alternatives to the DSA criterion in the diagnosis of ABMR. Evidence in support of incorporation into the classification of 2 such alternative markers, C4d and molecular ABMR assessment[17-20] consisting of either a set of antibody-mediated tissue injury–associated genes, or a respective molecular classifier, was reviewed at the 2017 Banff conference and is summarized in the following section. In a postmeeting poll answered by 63 experts, incorporation of these markers into the Banff classification for ABMR was favored by a majority, and this is reflected in the revised criteria for the diagnosis of ABMR described in this 2017 revision (Table 5). As C4d positivity is now considered an alternative for DSA criterion in cases where DSA testing is not available or potentially false negative, all biopsy specimens showing at least focally positive C4d staining now fall into 1 of 3 diagnostic categories: active ABMR, chronic active ABMR, and C4d staining without histologic evidence of rejection (Table 5). The potentially confusing categories of "suspicious for active ABMR" and "suspicious for chronic active ABMR" are now eliminated. It should be stressed here that these new criteria allowing for the diagnosis of ABMR in the absence of *detectable* DSAs do not constitute recognition of "antibody-negative ABMR" in the sense that Banff 2013 first recognized C4d-negative ABMR. It is rather an acceptance of the fact that current DSA testing methods do not detect all antibodies that are potentially injurious to the allograft, including some non-HLA antibodies, and that using the alternative markers discussed next will allow us to diagnose and treat a small but significant subset of cases of ABMR where current DSA testing methods fall short or are not available. Finally, DSA testing remains strongly recommended in all cases with biopsy specimens meeting the morphologic criteria (criteria 1 and 2) for active or chronic active ABMR (Table 5), not only for ABMR diagnosis but also for risk stratification, evaluating the response to treatment and further patient monitoring. A minor consideration in the revised classification, discussed later, involves the removal of the word "acute" from "acute/active ABMR."

TABLE 4 References for gene lists

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(Continues)

TABLE 4 (Continued)

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Virus (virus-specific transcripts: BK, cytomegalovirus, Epstein–Barr virus)	Unpublished

ABMR, antibody-mediated rejection; TCMR, T cell–mediated rejection.
[a]Also contains housekeeping genes.

3.3 | Alternatives to the DSA criterion in ABMR diagnosis

Compared with the previous (2007) Banff classification for ABMR, in which peritubular capillary C4d staining was required in addition to microvascular inflammation (MVI; glomerulitis and/or peritubular capillaritis) and DSAs for the diagnosis of active ABMR,[21] the Banff 2013 classification,[14] which introduced C4d-negative ABMR, has a higher sensitivity for ABMR diagnosis and an improved association of ABMR diagnosis with graft outcome.[22] Furthermore, molecular studies of Gupta et al[23] strongly validated the MVI sum score of (g + ptc) ≥2 required for diagnosis of ABMR by Banff 2013. Still, MVI, even with (g + ptc) scores of ≥2 and as high as 5, is not specific for ABMR,[23,24] and Sis et al[24] found that 11% of patients with biopsy specimens showing (g + ptc) = 5 were DSA negative. Nevertheless, MVI remains strongly associated with graft outcomes,[25] and a

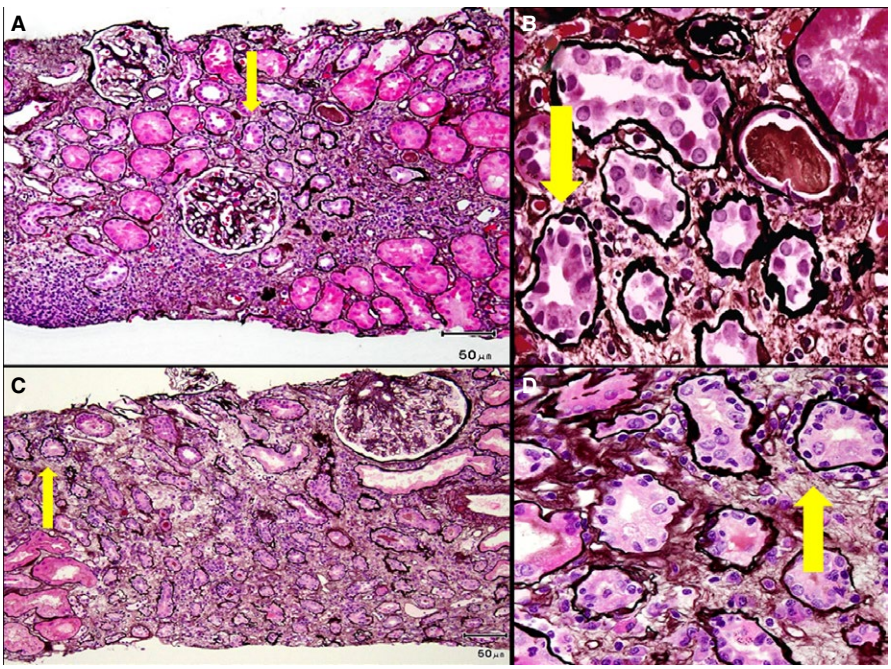

FIGURE 1 Representative cases of chronic active T cell–mediated rejection, grades 1A (A, B) and 1B (C, D). Each biopsy specimen shows widespread interstitial inflammation (mainly lymphocytes in A and B; lymphocytes with plasma cells in C and D) with accompanying interstitial edema in areas of the cortex with interstitial fibrosis and tubular atrophy (i-IFTA score 3). Both biopsy specimens also show tubulitis involving tubules with mild to moderate atrophic changes; this tubulitis is moderate (t2) in A and B and severe (t3) in C and D. There was also mild tubulitis (t1) in nonatrophic tubules in both biopsy specimens, and each specimen also had a total inflammation (ti) score of 2, although this cannot be determined from the photomicrographs. While both biopsy specimens show considerable edema associated with the inflammation, there is also interstitial fibrosis in these areas as is most evident from the darker staining areas of the interstitium in B and D. The yellow arrows indicate tubules with tubulitis; the tubules so indicated are the same tubules in the low-power and corresponding high-power photomicrographs (A, B; C, D). Jones methenamine silver stain; original magnification 100× (A, C) or 400× (B, D; scale bars in A and C indicate 50 µm)

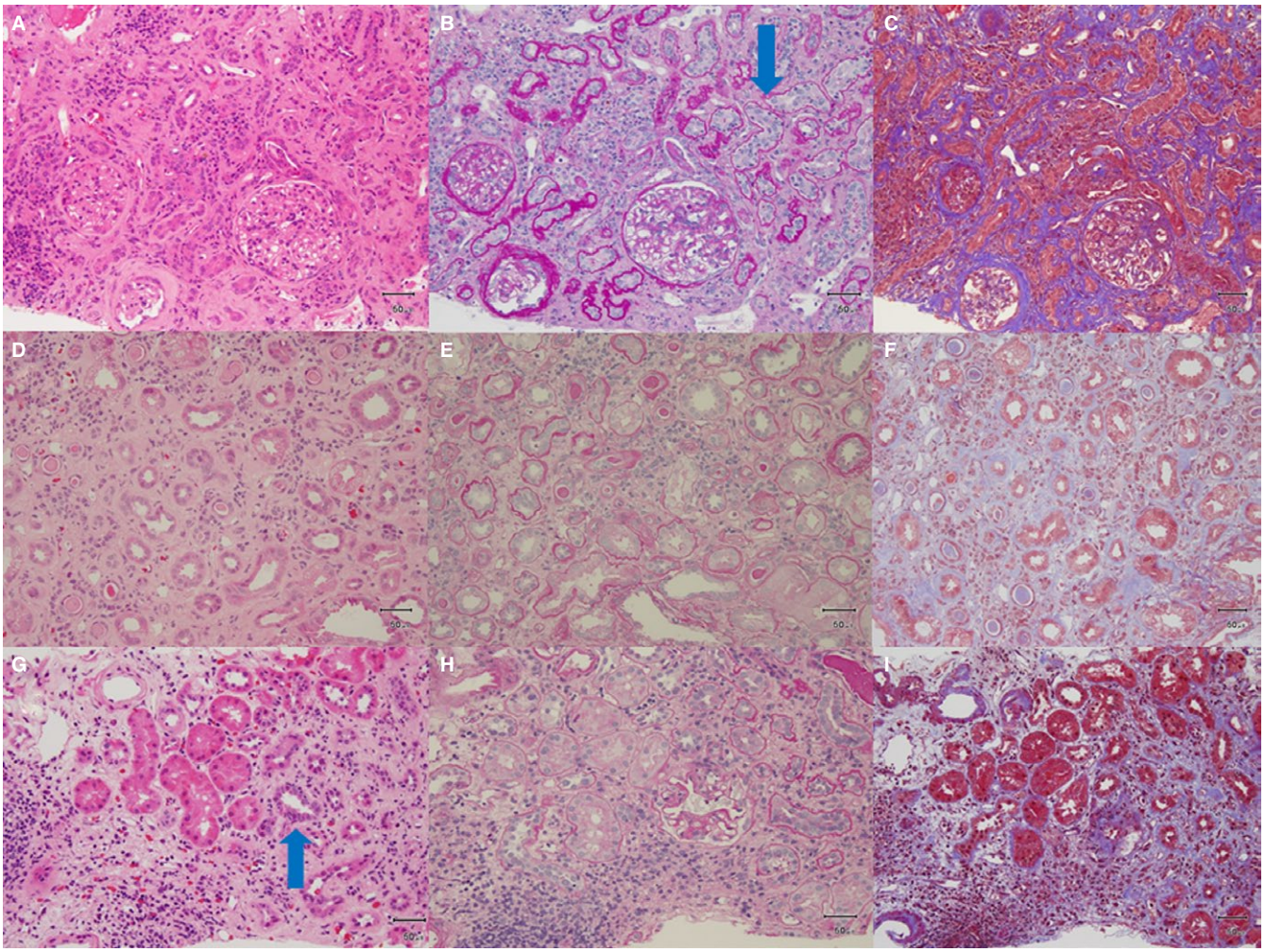

FIGURE 2 Three renal allograft biopsies specimens showing inflammation in areas of interstitial fibrosis and tubular atrophy (i-IFTA) with varying densities of interstitial fibrosis and degrees of interstitial inflammation, edema, and tubulitis, using 3 different histologic stains. The biopsy specimen in A-C shows dense interstitial fibrosis but also widespread and focally heavy inflammation in the sclerotic interstitium (i-IFTA 3) with tubulitis involving several mildly to moderately atrophic tubules, up to score t3 (arrow, B). The biopsy specimen in D-F also shows dense interstitial fibrosis, but milder inflammation. Although the inflammation in D-F is fairly diffuse, this was not true in other areas of cortex with fibrosis, and the i-IFTA score on this biopsy was 2. In addition, there is only mild tubulitis (t1), and as such, this biopsy specimen did not meet criteria for chronic active T cell–mediated rejection. In the biopsy specimen in G-I, the interstitial fibrosis is focally dense and focally less so with interstitial edema, as is most evident on the trichrome stain in I. There is more variable inflammation (overall i-IFTA score was 2), although t2 tubulitis is evident in a mildly atrophic tubule (arrow, G). Hematoxylin and eosin (H&E; A, D, G), periodic acid–Schiff (PAS; B, E, H), and Masson trichrome (C, F, I) stains; original magnification 200× (all panels). The scale bar at the bottom right of each panel indicates 50 μm

problem with clinical application of the Banff 2013/2015 criteria remains what should be done in cases where there are no detectable DSAs but a biopsy specimen otherwise meeting criteria for ABMR (MVI score ≥1 and C4d-positive; MVI score ≥2 and C4d negative). In such instances, testing for non-HLA antibodies (eg, anti–angiotensin type 1 receptor) is strongly advised, although such testing is not done at all centers and the clinical implications of such antibodies are not completely understood. While the limited sensitivity of C4d in the diagnosis of ABMR is well recognized and led to the incorporation of C4d-negative ABMR into the Banff classification in 2013,[14] multiple studies have shown that C4d staining in peritubular capillaries by immunofluorescence (IF) on frozen sections or immunoperoxidase on paraffin sections has a very high (>90%) specificity for the presence of DSAs if positive.[26-28] False-positive C4d staining in peritubular capillaries was not seen in studies of native renal biopsy specimens or preimplantation biopsy specimens of donor kidneys.[29,30] Accordingly, it was agreed that C4d staining in at least 10% of peritubular capillaries (C4d2 or C4d3) by IF on frozen sections or in any peritubular capillaries by immunoperoxidase on paraffin sections (C4d score >0) should be regarded as sufficient for the diagnosis of ABMR in the presence of MVI (ie, meeting criterion 3 of the classification), regardless of whether detectable DSAs are present (Table 5).

We also considered possible molecular alternatives to the DSA criterion. Molecular markers, in the form of those associated with endothelial injury, were first introduced into criterion 2 of the

TABLE 5 Revised Banff 2017 classification of antibody-mediated rejection (ABMR) and T cell–mediated rejection (TCMR) in renal allografts: revisions highlighted in boldface type

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)[1] 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 (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 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[2]	
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 (requires EM)[3] Arterial intimal fibrosis of new onset, excluding other causes; leukocytes within the sclerotic intima favor 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	
C4d Staining without Evidence of Rejection; all 4 features must be present for diagnosis[4]	
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 changes	
Suspicious (Borderline) for acute TCMR	
Foci of tubulitis (t > 0) with minor interstitial inflammation (i0 or i1), or moderate-severe interstitial inflammation (i2 or i3) with mild (t1) tubulitis; retaining the i1 threshold for borderline with t > 0 is permitted although this must be made transparent in reports and publications	
No intimal or transmural arteritis (v = 0)	
Category 4: TCMR	
Acute TCMR	
Grade IA	Interstitial inflammation involving >25% of nonsclerotic cortical parenchyma (i2 or i3) with moderate tubulitis (t2) involving 1 or more tubules, not including tubules that are severely atrophic[5]
Grade IB	Interstitial inflammation involving >25% of nonsclerotic cortical parenchyma (i2 or i3) with severe tubulitis (t3) involving 1 or more tubules, not including tubules that are severely atrophic[5]
Grade IIA[1]	Mild to moderate intimal arteritis (v1), with or without interstitial inflammation and/or tubulitis
Grade IIB[1]	Severe intimal arteritis (v2), with or without interstitial inflammation and/or tubulitis
Grade III[1]	Transmural arteritis and/or arterial fibrinoid necrosis of medial smooth muscle with accompanying mononuclear cell intimal arteritis (v3), with or without interstitial inflammation and/or tubulitis

(Continues)

TABLE 5 (Continued)

Chronic Active TCMR	
Grade IA	**Interstitial inflammation involving >25% of the total cortex (ti score 2 or 3) and >25% of the sclerotic cortical parenchyma (i-IFTA score 2 or 3) with moderate tubulitis (t2) involving 1 or more tubules, not including severely atrophic tubules[5]; other known causes of i-IFTA should be ruled out**
Grade IB	**Interstitial inflammation involving >25% of the total cortex (ti score 2 or 3) and >25% of the sclerotic cortical parenchyma (i-IFTA score 2 or 3) with severe tubulitis (t3) involving 1 or more tubules, not including severely atrophic tubules[5]; other known causes of i-IFTA should be ruled out**
Grade II[1]	**Chronic allograft arteriopathy (arterial intimal fibrosis with mononuclear cell inflammation in fibrosis and formation of neointima)**

Updates from Banff 2015[1] are indicated in boldface type.

[1]It should be noted that these arterial lesions may be indicative of ABMR, TCMR, or mixed ABMR/TCMR. "v" lesions and chronic allograft arteriopathy are only scored in arteries having a continuous media with ≥2 smooth muscle layers.

[2]Lesions of chronic active ABMR can range from primarily active lesions with early transplant glomerulopathy (TG) evident only by EM (cg1a) to those with advanced TG and other chronic changes in addition to active microvascular inflammation. For biopsy specimens showing TG and/or peritubular capillary basement membrane multilayering in the absence of evidence of current/recent antibody interaction with the endothelium (criterion 2) but with a prior documented diagnosis of active or chronic active ABMR or documented prior evidence of DSA, the term "chronic ABMR" should be applied.

[3]Indicates ≥7 layers in 1 cortical peritubular capillary and ≥5 in 2 additional capillaries, avoiding portions cut tangentially.

[4]The clinical significance of these findings may be quite different in grafts exposed to anti–blood group antibodies (ABO-incompatible allografts), where they do not appear to be injurious to the graft and may represent accommodation. However, with anti-HLA antibodies, such lesions may progress to chronic ABMR, and more outcome data are needed.

[5]A severely atrophic tubule is defined as one with each of the following 3 features: a diameter <25% of that of unaffected or minimally affected tubules on the biopsy, an undifferentiated-appearing, cuboidal or flattened epithelium, and pronounced wrinkling and/or thickening of the tubular basement membrane.

ABMR classification in Banff 2013.[14] Since that time, combinations of transcripts have been introduced with far greater specificity for ABMR,[17-20] although these molecular tests admittedly still have limitations and are not yet approved as diagnostic tests by regulatory bodies. Hidalgo et al[31] introduced a "DSA-specific" transcript set (DSASTs) of mRNAs differentially expressed in biopsy specimens from DSA-positive and DSA-negative patients, excluding those differentially expressed in rejecting versus nonrejecting biopsy specimens, although these studies showed DSASTs to be more of a marker for ABMR than for the presence of DSAs.[31] A more specific molecular marker for ABMR is the ABMR classifier,[17-20] consisting of 30 nonredundant probes, selected from comparisons between biopsy specimens with versus those without histologic changes of ABMR. Data from Loupy et al[19] showed that adding the results of the ABMR classifier to histologic findings significantly improved their ability to diagnose ABMR, independently from C4d and DSA. Therefore, despite the limitations noted, it was thought that this classifier or a related gene set could potentially be used to satisfy criterion 3 in the diagnosis of ABMR, similar to C4d (Table 5). It should be stressed that for this to be done at any given center, the cut-off value of such molecular assessment in the diagnosis of ABMR must be independently validated at each center at this point in time. With technologies becoming available to derive the molecular assessment (classifier or gene set) from formalin-fixed paraffin-embedded (FFPE) routine biopsy specimens,[32,33] multicenter validation should become feasible in the near future through collaborative efforts of the ongoing Banff working groups (Table 1).

3.4 | Removal of the term "acute" from "acute/active ABMR"

In Table 2 of the 2013 Banff Classification,[14] it is noted in a footnote that lesions classified as acute/active ABMR may be clinically acute, smoldering, or subclinical; this qualifier was also maintained in the 2015 revision.[1] Thus, the use of the word "acute" in the term "acute/active ABMR" can be misleading, and it was elected to simply refer to lesions of ABMR with microvascular injury and evidence of current or recent antibody interaction with graft endothelium but without morphologic evidence of chronic vascular injury (transplant glomerulopathy [TG], peritubular capillary basement membrane multilayering [PTCBML], new-onset arterial intimal fibrosis [cv]), simply as *active ABMR*, keeping the footnote from Banff 2013 (Table 5). A majority (62%) of meeting attendees responding to the survey agreed. However, the rationale for this change goes beyond simply clarifying terminology and also considers the likelihood that there are multiple clinicopathologic forms of active ABMR. At a minimum, these include true acute ABMR, typically presenting with acute graft dysfunction in highly sensitized graft recipients having a memory humoral response, presenting early posttransplantation without chronic damage to the

TABLE 6 Recommended indications for use of molecular diagnostics in renal allograft biopsy diagnosis

Histology/Banff scores/serology	Differential diagnosis	Possible molecular test
Mild MVI (g + ptc = 1) C4d negative, DSA positive	ABMR vs no ABMR	ABMR classifier[17,40] DSAST[31,41]
Moderate to severe peritubular capillaritis (ptc ≥2) No glomerulitis (g = 0) TCMR or borderline C4d negative, DSA positive	Pure TCMR/borderline vs mixed ABMR + TCMR/borderline	ABMR classifier[17,40] DSAST[31,41]
Moderate to severe MVI (g + ptc ≥2) C4d negative No identifiable anti-HLA DSA, ± non-HLA antibody	ABMR vs no ABMR	ABMR classifier[17,40] DSAST[31,41]
No MVI (g + ptc = 0) C4d positive, ± DSA ABO compatible	ABMR vs no ABMR	ABMR classifier[17,40] DSAST[31,41]
MVI (g + ptc > 0); C4d positive no identifiable anti-HLA DSA ABO incompatible	ABMR vs no ABMR	ABMR classifier[17,40] DSAST[31,41]
TG (cg > 0) No or mild MVI (g + ptc ≤ 1) C4d negative, DSA positive	Purely chronic ABMR or no ABMR vs chronic active ABMR	ABMR classifier[17,40] DSAST[31,41]
Borderline infiltrate	TCMR vs no TCMR	TCMR classifier[42,43]
Isolated arteritis (no MVI or TCMR) C4d negative, ± DSA	TCMR vs ABMR vs mixed rejection vs no rejection	ABMR classifier[17,40] DSAST[31,41] TCMR Classifier[42,43]

ABMR, antibody-mediated rejection; ABO, blood group antigens; cg, Banff chronic glomerulopathy score; DSA, donor-specific antibody; DSAST, donor-specific antibody specific transcript; g, Banff glomerulitis score; MVI, microvascular inflammation; ptc, Banff peritubular capillaritis score; TCMR, T cell–mediated rejection; TG, transplant glomerulopathy.

allograft; smoldering active ABMR, which may be diagnosed on surveillance or indication biopsy specimens in patients who most often have low-level DSAs (de novo or persistent/recurrent); and chronic active ABMR, which most often represents a continuum of the smoldering form should the latter not be diagnosed and treated in a timely manner, frequently in patients with limited compliance. In contrast with true acute ABMR, which can often be reversed by a combination of current, standard-of-care treatments aimed primarily at removing DSAs (eg, plasmapheresis, rituximab, intravenous immunoglobulin),[34,35] smoldering active ABMR should be a major focus for future clinical trials of novel agents designed to treat active ABMR and prevent de novo or progressing TG by mechanisms other than (or in addition to) DSA removal. In summary, the word "active" in the pathology report indicates ongoing disease activity highlighted by MVI with or without concomitant chronic remodeling (TG, PTCBML, IFTA, cv) of the allograft.

3.5 | Recommendations for use of molecular diagnostics

Molecular diagnostics were first introduced into the Banff classification in 2013,[14] although this was limited to ABMR and its introduction was as much to encourage development of more specific and more universally applicable molecular tests as to be used in diagnosing ABMR at that time. That former goal has in fact come to fruition, and multiple groups in North America and Europe are now applying molecular diagnostics in analyzing renal allograft biopsy specimens[18-20]—as summarized in Tables 3 and 4. Just as the 2013 Banff meeting report[14] put forth recommendations regarding taking a sample of tissue from renal allograft biopsies for electron microscopy (EM) and guidelines for performing EM to detect early changes of transplant glomerulopathy (cg1a), it is now appropriate to recommend sampling of biopsy tissue for molecular studies and to provide guidelines for when such studies are likely to be helpful diagnostically (Table 6). The latter specifically include situations where a combination of histologic, immunohistologic, and serologic data remain equivocal for diagnosis of ABMR, such as when the biopsy shows microvascular inflammation (g + ptc ≥ 2) but no C4d and there are no detectable DSAs; in biopsy specimens of ABO-incompatible allografts showing (g + ptc ≥ 2) and where a positive C4d is not helpful diagnostically[36]; and in biopsy specimens of ABO-compatible grafts where there is C4d positivity and DSA but no histologic evidence of rejection. In addition, testing for transcript sets strongly associated with TCMR[15,16,18,20] may also prove useful in differentiating borderline infiltrates likely to lead to development of overt TCMR and/or graft fibrosis from those that are not, as well as evaluating

the thresholds values for chronic active TCMR introduced in this report (Table 5).

It should be noted that at this point no specific Banff recommendations are given regarding which molecular classifiers/transcript sets should be tested for or the platform(s) used to assess gene expression. This includes the decision whether to perform molecular studies on freshly sampled tissue or FFPE,[32,33] the latter having the advantage of being done on the same tissue used for routine histology but with possible reduced sensitivity due to RNA degradation during processing. In all cases, molecular analyses need to be validated in any individual laboratory performing such testing, and gene expression thresholds significantly associated with ABMR, TCMR, or other lesions may well be different in different laboratories using the same transcript sets and platforms. As mentioned, because there are no specific lesions for ABMR/TCMR, no specific gene would be per se relevant for discrimination these diseases. A holistic molecular approach using machine learning and classifiers has been done in recent years and has provided valuable information for improving the classification and prognostic assessment of rejection.[19,37-39]

As discussed, the changes made to the Banff classification in 2013[14] stimulated many studies that largely validated those changes but also led to additional modification of the classification presented in the 2015 meeting report[1] and here. Similarly, it is anticipated that the changes and recommendations made in this meeting report will serve as a stimulus for studies testing the validity of the revised diagnostic criteria for TCMR and ABMR with respect to predicting patient outcomes, as well as studies directly applying molecular diagnostics in the clinical setting along the path toward molecular consensus described in the 2015 Banff meeting report.[1] The ultimate goals are not only to improve our ability to predict graft outcomes but also to better guide therapy, including in those cases where histology and serology alone cannot optimally do so, leading to improved patient outcomes compared with the current standard of care.

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