

ORIGINAL ARTICLE**Banff survey on antibody-mediated rejection clinical practices in kidney transplantation: Diagnostic misinterpretation has potential therapeutic implications**

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The aim of this study was to determine how the Banff antibody-mediated rejection (ABMR) classification for kidney transplantation is interpreted in practice and affects therapy. The Banff Antibody-Mediated Injury Workgroup electronically surveyed clinicians and pathologists worldwide regarding diagnosis and treatment for 6 case-based scenarios. The participants' (95 clinicians and 72 renal pathologists) assigned diagnoses were compared to the Banff intended diagnoses (reference standard). The assigned diagnoses and reference standard differed by 26.1% (SD 28.1%) for

pathologists and 34.5% (SD 23.3%) for clinicians. The greatest discordance between the reference standard and clinicians' diagnosis was when histologic features of ABMR were present but donor-specific antibody was undetected (49.4% [43/87]). For pathologists, the greatest discordance was in the case of acute/active ABMR C4d staining negative in a positive crossmatch transplant recipient (33.8% [23/68]). Treatment approaches were heterogeneous but linked to the assigned diagnosis. When acute/active ABMR was diagnosed by the clinician, treatment was recommended 95.3% (SD 18.4%) of the time vs only 77.7% (SD 39.2%) of the time when chronic active ABMR was diagnosed ($P < .0001$). In conclusion, the Banff ABMR classification is vulnerable to misinterpretation, which potentially has patient management implications. Continued efforts are needed to improve the understanding and standardized application of ABMR classification in the transplant community.

KEYWORDS

classification systems: Banff classification, clinical decision making, clinical research/practice, kidney transplantation/nephrology, rejection: antibody-mediated (ABMR)

1 | INTRODUCTION

The ultimate goal of the Banff Foundation for Allograft Pathology is to optimize the outcomes of transplant recipients.¹ The universally accepted pathologic-based classification system for antibody-mediated rejection (ABMR) formulated by Banff has been a major advancement in the field to increase the awareness of ABMR as an entity and standardize definitions.² However, it remains unclear how the Banff classification system for kidney ABMR is actually used or interpreted in practice. Understanding how classification systems are interpreted is critically important because misuse or confusion of diagnostic criteria can have major clinical implications, including the omission or unnecessary administration of treatment. Therapeutic development is also dependent on a clear diagnostic classification system because of its influence on patient inclusion into clinical trials. An ideal disease classification system would be reproducible, reflect the underlying biological process, provide prognostic information, and have a consistent and widespread use.

The Banff diagnostic schema of ABMR is a combination of serologic (circulating donor-specific antibody [DSA]), histologic (primarily microvascular inflammation and transplant glomerulopathy), and immunohistologic (C4d staining in peritubular capillaries) criteria.² The Banff Antibody-Mediated Injury Working group (Banff AMI-WG), which was previously known as the Highly Sensitized workgroup, was formed at the Banff 2013 Conference in Comandantuba, Brazil with the goal to propose recommendations for improving ABMR nomenclature based on pathophysiology and clinical practice.^{2,3} This workgroup is distinctive because it is composed of a multidisciplinary team of transplant clinicians, pathologists, immunologists, and histocompatibility lab directors to consider the complex interplay of the bedside evaluation, allograft histology, and DSA characteristics.

The aim of this project was 2-fold: (1) to determine how Banff nomenclature is interpreted in practice, specifically by clinicians at the bedside and by renal pathologists and (2) to understand how patients with ABMR are managed in clinical practice based upon Banff classification of their pathology. To achieve these goals, a survey was sent to an international group of kidney transplant nephrologists, transplant surgeons, and renal pathologists. All participants were asked to select a diagnosis for 6 common postkidney transplant clinical scenarios. The clinician group was also asked to select a treatment approach.

2 | METHODS

We performed an international survey of transplant clinicians (nephrologists/transplant surgeons) and renal pathologists to determine how Banff nomenclature^{2,3} is interpreted in practice and affects therapeutic decision making. The study was approved by the Mayo Clinic Research Ethics Board (Rochester, MN).

The survey was distributed by email to members of the American Society of Transplantation – Kidney/Pancreas Community of Practice, the Canadian Society of Transplantation, the Canadian Society of Nephrology, the Canadian National Transplantation Research Network, and the European Kidney Transplant Association (EKITA; section of the European Society of Transplantation). The survey was also distributed as an announcement in the Weekly Tribune of the Transplantation Society. The survey was administered from September 2016 through August 2017 (prior to the updated Banff 2017 classification that removed acute from acute/active ABMR classification⁴). The authors (CAS and LDC) of the manuscript also sent emails to 437 personal nephrologist/surgeon contacts. To maximize the response rate, a

follow-up email/announcement by each of the societies was sent at least once after a 2-week interval. To capture additional renal pathologists' responses, the survey was distributed to all members of the Renal Pathology Society. We asked the respondents to provide their name and contact information to exclude duplicate responses, but this was not required.

Transplant clinicians (nephrologists and surgeons) and pathologists were given 6 common clinical scenarios and were asked to select a diagnosis. The 6 clinical scenarios were written to represent cases commonly encountered in clinical practice including (1) chronic active ABMR with de novo DSA and positive C4d staining, (2) acute/active ABMR with de novo DSA and negative C4d staining, (3) chronic active ABMR but negative C4d staining with de novo DSA, (4) histologic features of ABMR without detectable anti-Human Leukocyte Antigen (HLA) antibody, (5) acute/active ABMR with negative C4d

staining in the setting of a positive crossmatch transplant and detectable DSA, and (6) mixed acute T cell-mediated rejection (a-TCMR) and ABMR with de novo DSA (Figure 1). The diagnostic choices differed based on scenario but included the following: acute/active ABMR, chronic active ABMR, no ABMR, depends on non-HLA DSA testing, a-TCMR, mixed a-TCMR and C4d negative ABMR, and other (specify) (Tables S1-S6). Transplant clinicians were also asked to select a recommended treatment regimen. For all questions, participants were given the opportunity to select "Other" as a response to diagnostic and therapeutic questions and provide supplementary free text. All free text "other" responses were reviewed by author (CAS). If the free text was essentially the same as one of the multiple choice categories, the response was reclassified to reflect that. If free text was clearly different than the choices presented, the response was considered "other."

FIGURE 1 Survey case-based scenarios. Pathologists and clinicians were provided the scenarios with multiple diagnoses to choose from. The diagnostic choices included (1) acute/active antibody-mediated rejection (ABMR), (2) chronic active ABMR, (3) no ABMR, and (4) other (with opportunity for free text diagnosis). Case 4 also included Depends on whether testing for non-HLA donor-specific antibody (DSA) identified. Case 6 included 2 other choices: (1) combined T cell-mediated rejection and ABMR and (2) T cell-mediated rejection only. The reference standard diagnoses were the following: Case 1 – Chronic active ABMR, Case 2 – Acute/active ABMR, Case 3 – Chronic active ABMR, Case 4 – Depends on whether testing for non-HLA DSA identified, Case 5 – Acute/active ABMR, and Case 6 – Mixed acute T cell mediated rejection and ABMR. cg, chronic glomerulopathy

Case 1: Chronic active ABMR with de novo DSA and positive C4d

Mr. Smith is a 54-year-old male who received a 5/6 HLA mismatch negative flow cytometric crossmatch kidney transplant 4 years ago. No donor-specific antibody was identified pretransplant. His baseline creatinine was 1.5mg/dl (132.63 umol/L). He has not had labs in the last 6 months. He comes to clinic feeling well and has had no major health events over the last year, but his creatinine is up to 2.2mg/dl (194.52 umol/L). He has class I and class II DSA (A2 – MFI 2000 and DQ7 of 3000). He has mild proteinuria with protein/creatinine ratio of 0.3. A renal biopsy was performed showing glomerulitis (Banff g score 2), peritubular capillaritis (Banff ptc score 1), mild transplant glomerulopathy (cg score 1), and positive C4d. There is no active interstitial inflammation, tubulitis, or interstitial fibrosis/tubular atrophy.

Case 2: Acute/active ABMR with de novo DSA and negative C4d

Ms. Jones is 25-year-old female who received 4/6 HLA mismatch negative flow cytometric crossmatch kidney transplant 3 years ago. She did not have any donor-specific antibodies at the time of transplantation. Her baseline creatinine was 0.8 mg/dl (70.74umol/L), but has been gradually increasing over the last 6 months. It is now up to 1.4mg/dl (123.79 umol/L). Her post-transplant course has been remarkable for an acute cellular rejection at 6 months posttransplant that was treated. Your center does not do surveillance biopsies or DSA testing. Because of the increased creatinine, DSA was obtained and was positive (DQ7 - MFI 4000). She does not have any proteinuria. Kidney biopsy shows peritubular capillaritis (ptc 2), glomerulitis (g score 1), and C4d is negative. There is no interstitial inflammation, tubulitis, transplant glomerulopathy, or tubular atrophy.

Case 3: Chronic active ABMR with de novo DSA and negative C4d

Mr. White is a 45-year-old male with a history of a deceased donor negative cytotoxic crossmatch kidney transplant 10 years ago. It is unknown whether he has any baseline donor-specific antibody. His post transplant course has been relatively unremarkable. His baseline creatinine is 1.5mg/dl (132.63 umol/L) and at a routine follow-up, you find that his creatinine is up to 2.2mg/dl (194.52 umol/L). Urine protein to creatinine ratio is 0.5. Patient is found to have donor-specific antibody - DQ6 with an MFI of 3000. Kidney biopsy shows peritubular capillaritis (ptc score 2), glomerulitis (g score 1), mild transplant glomerulopathy (cg score 1) and C4d is negative. There is no interstitial inflammation, tubulitis, interstitial fibrosis, or tubular atrophy.

Case 4: Histologic features of ABMR without detectable anti-HLA antibody

Ms. Moore is a 62-year-old female with a history of 2 failed kidney transplants. She received a negative flow cytometric crossmatch deceased donor kidney transplant 1 year ago. No donor-specific antibody was identified at the time of transplantation. She comes for routine follow-up visit. Her creatinine is stable at 1.7mg/dl (150.31 umol/L). Her protein to creatinine ratio is 0.6. She does not have any donor-specific antibody. Kidney biopsy shows peritubular capillaritis (ptc 2), glomerulitis (g score 2) and C4d is negative. There is no interstitial inflammation, tubulitis, interstitial fibrosis, or tubular atrophy.

Case 5: Acute/ active ABMR with negative C4d in setting of Positive Crossmatch Transplant and Positive DSA

Mr. Philips is a 56-year-old male with a history of 2 failed kidney transplants. He received a low positive flow cytometric crossmatch (negative CDC crossmatch) deceased donor kidney transplant 6 months ago. Donor-specific antibody was identified at the time of transplant (A2 MFI – 2500 and DQ2 MFI – 3500). He comes for routine follow-up visit. His creatinine is stable at 1.7mg/dl (150.31 umol/L). His protein to creatinine ratio is 0.6. He continues to have donor-specific antibody (A2 MFI – 1500 and DQ2 MFI – 4500). Kidney biopsy shows peritubular capillaritis (ptc score 2), glomerulitis (g score 2) and C4d is negative. There is no interstitial inflammation, tubulitis, interstitial fibrosis, or tubular atrophy.

Case 6: Mixed acute T cell mediated rejection and ABMR

Mr. Low is a 35-year-old male who received a negative flow cytometric crossmatch deceased donor kidney transplant 18 months ago. No donor-specific antibody was identified at the time of transplant. He comes in for an urgent visit. His creatinine is up to 2.5mg/dl (221.05 umol/L) from baseline of 1.5mg/dl (132.63 umol/L). Protein/creatinine ratio is 0.2. New donor-specific antibody was identified (A2 MFI – 2500 and DQ2 MFI – 3500). Kidney biopsy shows peritubular capillaritis (ptc score 2), glomerulitis (g score 1), no transplant glomerulopathy (cg score 0), and C4d is negative. There is also interstitial inflammation and tubulitis consistent with a Banff grade 1B acute cellular rejection.

We provide descriptive statistics on the distribution of diagnoses assigned by the survey participants. For the purposes of this study, the diagnosis chosen by the survey participant was referred to as the assigned diagnosis and the diagnosis agreed upon by the Banff AMI-WG (CAS, MN, LDC, and RSP) was considered the reference standard. Chi-square tests were used to compare categorical data among survey participants for each case. Unanswered questions were excluded from the analysis of discordant diagnoses. Matched pair analysis was used to compare the treatment choices for acute/active ABMR and chronic active ABMR among clinician respondents only. All analyses were performed with JMP software version 13 (Cary, NC).

3 | RESULTS

3.1 | Survey respondent characteristics

We received results from 83 pathologists of the 536 who were contacted through an email from the Renal Pathology Society (15.5% response rate). Within this group, 11 responses were excluded ($n = 6$ no questions answered and $n = 5$ from duplicate respondents), and therefore a total of 72 responses from the pathologist group were analyzed. Ninety-six responses were obtained from the clinician group, and of those only one was excluded (duplicate response). The survey was sent directly by email to 437 clinicians (personal contacts) and to an unknown number of potential respondents from the professional societies named in the Methods section (response rate approximated at 9.5% [95/1000]).

Five continents were represented in the pathologist survey (Figure 2A). The largest proportion of which were from North

American countries 43.1% (31/72). A total of 13.9% (10/72) of respondents were from Europe. In the clinician group, 6 of the 7 continents were represented (Figure 2B). Sixty-one percent (61.0% [58/95]) of respondents were from North America, and 26.3% (25/95) were from Europe. Transplant programs of all sizes (< 50 transplants per year up to > 200 transplants per year) were also represented by both pathologists and clinicians (Figure 2C,D).

3.2 | Discordance between respondents diagnoses and reference standard

The diagnosis assigned by the respondent and reference standard differed on average in 26.1% (SD 28.0%) of the cases per pathologist and 34.5% (SD 23.3%) of the cases per clinician ($P = .004$) (Table 1). Among pathologists, the discordance between the assigned diagnosis and reference standard was greatest for the scenario in which the histology showed acute/active ABMR with negative C4d staining in a patient who had received a positive crossmatch kidney transplant (case 5). Specifically, 33.8% (23/68) of pathologists assigned a diagnosis that differed from the reference standard. The greatest discordance between the assigned diagnosis and the reference standard in the clinician group was when histologic features of ABMR were present, but anti-HLA antibody was not identified (Case 4). When presented with this scenario, 49.4% (43/87) of clinicians assigned a diagnosis that was different from the reference standard (Table 1).

The assigned diagnosis by pathologists and clinicians had the greatest concordance with the reference standard in the case of mixed a-TCMR and ABMR in the setting of de novo DSA (case 6).

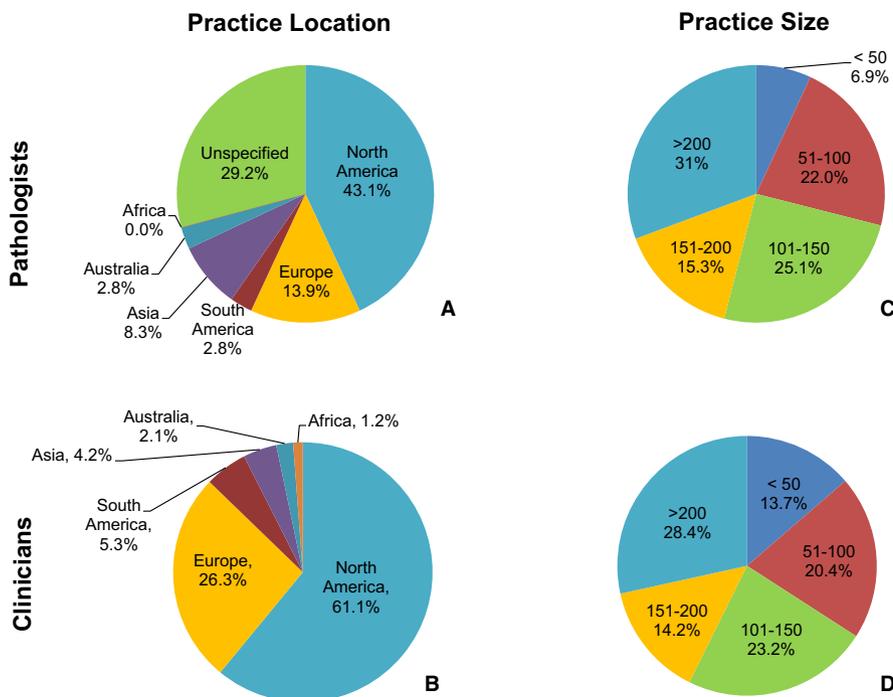


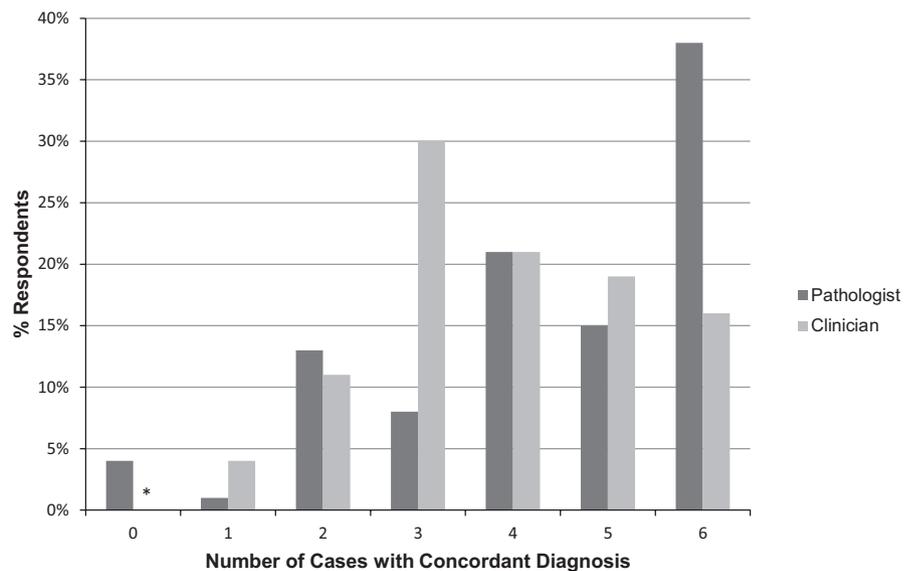
FIGURE 2 Location and size of respondents' affiliated transplant practice

TABLE 1 Interpretation of Banff ABMR classification in clinical practice

Scenario		% (n/N) of cases the respondents' assigned diagnosis differed from the reference standard (intended Banff diagnosis)		
		Pathologists	Clinicians	P value
Case 1	Chronic active ABMR with de novo DSA and positive C4d	27.8% (20/72)	46.3% (44/95)	.02
Case 2	Acute/active ABMR with de novo DSA and negative C4d	22.9% (16/70)	34.7% (33/95)	.14
Case 3	Chronic active ABMR with de novo DSA and negative C4d	27.5% (19/69)	24.2% (23/95)	.76
Case 4	Histologic features of ABMR without detectable anti-HLA antibody	20.6% (14/68)	49.4% (43/87)	.0004
Case 5	Acute/active ABMR with negative C4d in setting of positive crossmatch transplant and positive DSA	33.8% (23/68)	44.2% (42/95)	.24
Case 6	Mixed T cell-mediated rejection and C4d negative ABMR	14.7% (10/68)	10.6% (10/94)	.59
Mean (SD) number of cases/respondent		26.1% (SD 28.1%)	34.5% (SD 23.3%)	.04

ABMR, antibody-mediated rejection; DSA, donor-specific antibody.

FIGURE 3 Distribution of concordant assigned diagnosis and reference standard stratified by specialty. The percentage of respondents whose assigned diagnosis matched the reference standard in zero (0) to six (6) of the presented cases. *No clinician respondents assigned diagnoses that were different from the reference standard for all 6 cases



Specifically, 14.7% (10/68) of pathologists and 10.6% (10/94) of clinicians assigned a diagnosis that was different from the reference standard for this case. The respondents' assigned diagnosis for each of the clinical scenarios is presented in Tables S1-S6.

Among the pathologists surveyed, 37.5% (27/72) assigned diagnoses that were concordant with the reference standard for all 6 cases, and 4.2% (3/72) assigned diagnoses that were discordant for all 6 cases (Figure 3). In contrast, only 15.7% (15/95) of the clinicians assigned diagnoses that were concordant with the reference standard for all six cases, whereas zero (0% [0/95]) clinician respondents assigned discordant diagnoses for all cases. The largest proportion of clinicians (29.5% [28/95]) assigned diagnoses that were concordant with the reference standard only half of the time (3/6 cases).

3.3 | Factors related to discordance

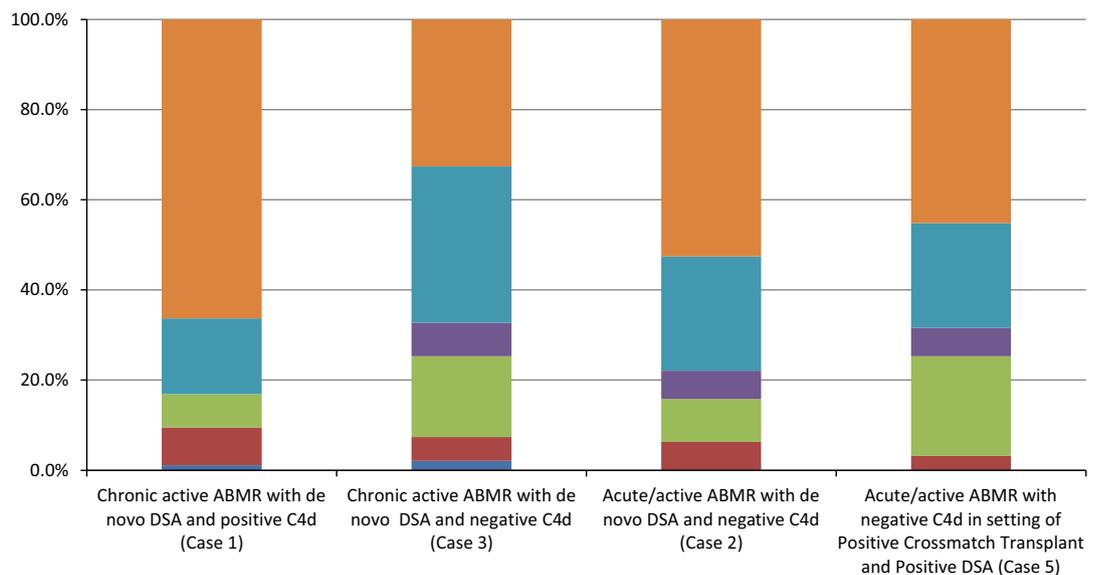
Affiliation with a small (< 100 transplants/year) transplant center was associated with a discordant assigned diagnosis and reference standard in the pathologist group. Specifically, among the assigned diagnoses by pathologists whose affiliated transplant center volume was equal or less than 100 transplants/year; 32.8% (39/119) were different from the reference standard, compared to only 21.3% (63/296) of diagnoses assigned by pathologists whose affiliated transplant center volume was greater than 100 transplants/year ($P = .01$). The presence of a Banff chronic glomerulopathy score > 0, allograft dysfunction, C4d positivity, location of transplant center, or de novo DSA were not associated with a discordant assigned diagnosis and reference standard among pathologists.

Among clinicians, the main factors associated with a discordant assigned diagnosis and reference standard were C4d staining positivity, stable allograft function, and size of transplant center. Among the C4d staining positive cases, 46.3% (44/95) of clinicians' assigned diagnoses were different from the reference standard. However, among the C4d staining negative cases, 32.4% (151/466) of clinician assigned diagnoses were different from the reference standard ($P = .01$ when compared to C4d positive cases). Of cases that were presented to clinicians who practiced at a transplant center performing less than or equal to 100 transplants/year, 40.5% (77/190) were discordant vs 31.8% (118/371) of cases presented to clinicians who practiced at a larger center, $P = .04$. When allograft function was stable, 46.7% (85/182) of assigned diagnoses were different from reference standard as compared to 29.0% (110/369) of cases in which allograft dysfunction function was present, $P < .0001$. Banff chronic glomerulopathy score > 0 , de novo DSA, and location of transplant center were not associated with discordance between the assigned diagnosis and the reference standard among the clinician group.

3.4 | Clinician treatment choices

Clinicians chose a variety of therapeutic approaches for each of the cases as detailed in Tables S1-S6. Importantly, the chosen therapeutic approach differed when the assigned diagnosis was the same (chronic active ABMR [cases 1 and 3] or acute/active ABMR [cases 2 and 5]) as shown in Figure 4. When the assigned diagnosis was chronic active ABMR, plasmapheresis-based therapy was chosen more frequently when C4d staining was positive (case 1) vs negative (case 3) [66.3% (63/95) vs 32.6% (31/95), $P < .0001$]. Conservative therapy (no specific therapy, optimize maintenance immunosuppression, or adjust antihypertensives) was recommended by only 7.4% (7/95) of clinicians' when C4d staining was positive (case 1) and by 17.9% (17/95) of clinicians when C4d staining was negative (case 3), $P = .05$.

The treatment approaches also differed between the 2 cases of acute/active ABMR with negative C4d staining. Although the majority of clinicians chose treatment with plasmapheresis, Intravenous Immunoglobulin (IVIg), and/or adjunctive therapies for both cases; more clinicians chose a conservative approach when the patient had



Treatment Choice	Case 1 (63/95)	Case 3 (31/95)	Case 2 (50/95)	Case 5 (43/95)
Plasmapheresis, IVIG, +/- rituximab and/or bortezomib	66.3% (63)	32.6% (31)	52.6% (50)	45.3% (43)
IVIG +/- steroids	16.8% (16)	34.7% (33)	25.3% (24)	23.2% (22)
Steroids only	0.0% (0)	7.4% (7)	6.3% (6)	6.3% (6)
Conservative treatment only	7.4% (7)	17.9% (17)	9.5% (9)	22.1% (21)
Other	8.4% (8)	5.3% (5)	6.3% (6)	3.2% (3)
Unanswered	1.1% (1)	2.1% (2)	0.0% (0)	0.0% (0)

FIGURE 4 Heterogeneity of clinicians' treatment choices. The treatment regimens were heterogeneous and differed among the cases ($P < .0001$) irrespective of the assigned diagnosis. The treatment choices offered for cases 1, 2, 3, and 5 were the same and included (A) conservative management (no specific therapy, optimize maintenance immunosuppression, or adjust antihypertensives); (B) steroids only, IVIG \pm steroids only; (C) plasmapheresis; (D) IVIG \pm adjunctive therapy (rituximab and/or bortezomib); and (E) other (with opportunity for free text diagnosis). Free text "other" responses included but not limited to a different combination of these therapies, rituximab or bortezomib alone, and tocilizumab. Additional therapeutic options were offered for cases 4 and 6 because of the context of these cases, and therefore they were not presented in this figure. See Tables S1-S6 for details. IVIG, Intravenous Immunoglobulin

DSA at the time of transplant (case 5) than when the DSA was de novo (case 2) (52.6% [50/95] vs 45.3% [43/95], $P = .38$). Only 9.5% (9/95) of clinicians chose conservative treatment in the setting of de novo DSA (case 2), whereas 22.1% (21/95) of clinicians chose conservative treatment in a positive crossmatch patient (case 5), $P = .03$.

Importantly, the assigned diagnosis (Banff interpretation by the clinician) was associated with the treatment choice. If the assigned diagnosis was ABMR (either acute/active or chronic active), treatment (steroids, IVIG, and/or plasmapheresis based therapy) was chosen for 87.7% (SD 23.3%) of the cases. The assigned diagnosis of acute/active ABMR was associated with treatment 95.3% (SD 18.4%) of the time. In contrast, when chronic active ABMR was assigned, treatment was recommended only 77.7% (SD 39.2%) of the time ($P < .0001$).

4 | DISCUSSION

Our study shows that a discrepancy exists in how Banff intended its ABMR classification system to be used and how it is actually interpreted in practice. Pathologists and clinicians alike assigned an ABMR diagnosis that was different from the Banff intended diagnosis approximately 30% of the time. This discrepancy is relevant because the diagnosis assigned by the clinician was associated with the corresponding treatment approach. We acknowledge the difficulty in drawing robust conclusions from survey data, but our results suggest the need for continued diligence to expand educational efforts to increase the awareness and understanding of the ABMR classification in the transplant community. Further enhancements in the ABMR diagnostic classification system itself may also be needed to increase its applicability and standardization.

Multiple factors likely explain the observed diagnostic discrepancies including the use of an outdated classification or misinterpretation of the current system, the decision not to use the Banff classification, or even the integration of factors not currently part of the Banff classification system (ie, allograft dysfunction) into the diagnosis. Some clinicians lack experience interpreting Banff scores because they routinely rely on the pathologists' final interpretation rather than the individual scores themselves. Moreover, the paucity of large well-designed therapeutic studies in the ABMR field may

also decrease the importance of the Banff ABMR classification for some clinicians and/or pathologists.

Another important finding was that treatment approaches for ABMR in general were heterogeneous. The scope of this heterogeneity is well illustrated in the case of chronic active ABMR that was C4d staining negative. Therapy with plasmapheresis and IVIG was recommended by 33.4% (33/95) of clinicians, and 17.9% (17/95) of clinicians chose a more conservative approach. However, when presented with a case of chronic active ABMR and C4d staining positivity, therapy with plasmapheresis and IVIG was recommended by 66.3% (63/95) of clinicians. Again, these results are likely a reflection of the fact that very few randomized clinical trials have been performed in ABMR⁵⁻⁷ and the available therapeutic regimens have questionable effectiveness.⁶⁻⁹ Center-specific practice patterns for ABMR management also likely influence treatment decisions. Beyond the relevance for individual patients, this heterogeneity must be considered when reviewing literature or comparing patient outcomes across centers because outcomes for patients with chronic active ABMR and active ABMR are often lumped together.

What is the path forward? The Banff participants are acutely aware of the need to increase the awareness and understanding of their classification systems. A new working group has been formed to specifically address the dissemination of Banff classification systems (Banff rules and dissemination working group),⁴ and our group has started collaborating. A central web-based repository of diagnostic parameters and definitions is being developed. Additionally, educational tools to standardize reporting of individual diagnostic features and automated computer algorithms to standardize diagnosis assignment may also be helpful. Formation of a Banff working group with the goal to improve the understanding of updated classification systems in the transplant community is also a consideration (Table 2).

Importantly, this survey preceded the updated Banff 2017 classification, which includes some important revisions, but it is unclear whether it would have modified the observed diagnostic discrepancies.⁴ First, the presence of detected DSA (anti-HLA or non-HLA) is no longer required for an ABMR diagnosis if C4d staining is positive in peritubular capillaries. We believe that this is an important change because of the high specificity for C4d staining

TABLE 2 Goals and next steps of the Banff antibody-mediated injury working group

Goal	Next steps
Increase the visibility and accessibility of updated Banff Classifications in the transplant community	Collaborate with the <i>Banff Rules and Dissemination Working group</i> on current projects to publicize changes to the ABMR classification
Improve the understanding of updated Banff classification systems in the transplant community	Propose that a Banff education workgroup be formed Develop an online case-based interactive educational module
<i>Long-term goal:</i> Provide recommendations to enhance the current diagnostic Banff ABMR classification system by incorporating prognostic features	<i>Long term:</i> Design and implement a multicenter prospective observational trial to validate single center predictive models for allograft survival based on a combination of histologic, serologic, molecular, and patient factors. Important prognostic factors could be integrated into diagnostic classification.

in peritubular capillary in diagnosing ABMR and the difficulty of testing for non-HLA antibodies in some settings and because unidentified pathologic anti-HLA antibodies also likely exist. Second, the term acute was removed from acute/active ABMR in the Banff 2017 ABMR classification system revision. The intent of this change was to minimize the confusion surrounding the timing of an ABMR episode because histologic findings of active ABMR, including C4d staining, peritubular capillaritis, and glomerulitis can be present for months to years without obvious evidence of allograft dysfunction or progression to transplant glomerulopathy.^{10,11} Subsequent studies requiring more detailed information about the clinical setting, time course, antibody characteristics and temporal change, and molecular data will be needed to determine whether these changes lead to more consistent diagnoses and treatments.

We acknowledge that incremental changes in the diagnostic classification system are an improvement but do not adequately address the major needs in this field. Minor changes in the language of the classification system itself will be helpful, but major research efforts are needed to move the Banff system from a discrete diagnostic platform to a prognostic classification system. Providing recommendations to enhance the current diagnostic Banff ABMR classification system by incorporating prognostic features is a long-term goal of our working group (Table 2). To move in this direction, several key knowledge gaps need to be addressed. First, a clear understanding of the natural histologic progression of ABMR in the setting of preformed and de novo DSA is critically needed to identify histologic, serologic, molecular, and/or clinical factors associated with inferior graft survival.¹² This will require a multicenter effort and close examination of both serial surveillance biopsies and clinically indicated biopsies in well-characterized patient cohorts who did and did not receive treatment. The information gleaned from this effort can be used to enhance models to predict long-term outcomes (progression to chronic active ABMR, allograft function decline, and allograft survival) for patients with ABMR. Optimally the important prognostic factors could be added to the Banff ABMR classification system to improve bedside patient care and effectively design therapeutic clinical trials.

Another challenge with the Banff classification system is the reproducibility of the renal histologic lesions central to the ABMR diagnosis. The interobserver variability and reproducibility of peritubular capillaritis, glomerulitis, and transplant glomerulopathy scoring are fair at best and the reproducibility of the ABMR diagnosis itself (the composite of peritubular capillaritis, glomerulitis, transplant glomerulopathy, and/or C4d) has not been well studied.¹³⁻¹⁸ Opportunity exists in developing innovative tools and methods to supplement histology for the diagnosis and prognosis of ABMR such as increased use of gene expression transcripts/classifiers.^{19,20}

The strength of our survey was the unique presentation of clinical scenarios similar to those seen in clinical practice and the survey of a diverse group of clinicians and renal pathologists who practice at transplant centers across the world. This is also the first study to examine how the Banff classification system is interpreted. However,

we recognize the limitations of our study given that we relied on survey data. Like other surveys, it was prone to response bias related to the voluntary nature of study participation. The response rate was also relatively low but larger and more comprehensive than similar surveys.²¹ The respondents were most likely invested in the diagnosis and treatment of ABMR, and thus the observed diagnostic discrepancies and treatment heterogeneity may underestimate the discrepancies and heterogeneity present in the wider transplant community. Some participants may have been approached more than once because of membership in multiple associations, but known duplicate responses were excluded. A perceived lack of anonymity may have influenced the responses. Additionally, the survey results were also largely descriptive. The study design and relatively low number of respondents limited our ability to consider factors that influenced diagnostic and treatment decisions in multivariable models.

In summary, the current Banff ABMR classification system is vulnerable to misinterpretation in clinical practice, which potentially has patient management implications. Continued efforts are needed to improve knowledge transfer and, consequently, the standardized application of the Banff ABMR classification in the transplant community. Major research efforts are needed in the ABMR field to inform the Banff group and move the current classification system from a discrete diagnostic platform to a prognostic classification system that can be used to inform effective patient care and clinical trial design.

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DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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