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Banff Antibody-Mediated Injury Working Grp

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ORIGINAL ARTICLE OPEN ACCESS

Rethinking the Diagnosis and Management of Antibody-Mediated Rejection in Multidisciplinary Transplant Meetings: A Global Survey and Banff Working Group Recommendations

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ABSTRACT

Introduction: The diagnosis of antibody-mediated rejection (AMR) requires input from several transplant professionals. Bringing clinical and laboratory experts together may help standardize care. Yet, little is known about current global practices of multidisciplinary meetings for AMR management.

Abbreviations: AMR, antibody-mediated rejection; dd-cfDNA, donor-derived cell free DNA; DSA, donor-specific antibodies; HLA, human leukocyte antigen; IS, immunosuppression; MMDx, molecular microscope; PGx, pharmacogenomics; Rx, treatment; VCA, vascularized composite allotransplant.

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Methods: The Banff Antibody-Mediated Injury Working Group approached professional societies worldwide to distribute a survey on the availability, content, participants, perceived value, and barriers to the implementation of multidisciplinary meetings.

Results: Four hundred two transplant professionals from six continents caring for kidney (90.55%), liver (21.14%), pancreas (20.65%), heart (15.17%), and lung (14.18%) transplant recipients participated in the survey, and 302 (75.12%) reported attending multidisciplinary meetings. Multidisciplinary meetings were more prevalent in academic centers, in high- versus low-to-middle-income regions (81.03% and 65.99%, respectively; $p < 0.001$), and in mid-to-large size transplant programs compared to smaller programs. Perceived value included continued professional development (97.68%) and trainee education (95.70%). AMR was reported to be discussed at these meetings by 217 respondents with case presentations reviewing patient characteristics, histology, and HLA antibody data. A third of the respondents reviewed non-HLA/pathogenic autoantibodies and/or molecular diagnostics, with the latter being more frequently applied in high- versus low-to-middle-income regions (46.71% and 12.31%, respectively; $p < 0.001$). AMR case presentations allowed diagnosis revision, actionable management plans and were perceived as improving care. The primary barrier to the implementation of multidisciplinary meetings (63.27%) was the unavailability of transplant professionals (e.g., transplant immunologists).

Conclusion: Facilitating multidisciplinary meetings through the remote participation of pertinent experts and incentivizing participation through remuneration, protected time, or continued medical education may help standardize AMR diagnosis and harmonize its management.

1 | Introduction

The care of transplant recipients is complex. It requires a collaborative and multidisciplinary effort, involving the coordination of healthcare professionals from a range of disciplines for the delivery of comprehensive care addressing the transplant recipient's medical, behavioral, and psychosocial needs. Multidisciplinary teams have been promoted to manage medical uncertainty and psychosocial risks. In the context of transplantation, multidisciplinary teams have also been engaged to ensure the equitable allocation of organs [1]. The growing transition toward international transparency as part of the global convergence on transplant practices [2] means increased adoption of multidisciplinary team frameworks within hospitals in the transplant context across the globe. Yet, despite calls for convergence and the realization of the need to standardize and harmonize approaches across borders, little is known by way of comparative analysis of approaches in different regions.

This knowledge gap gains greater importance as we consider the prevention and management of antibody-mediated rejection (AMR) [3–5]. As a diagnostic construct of predefined immunogenetic and histological criteria attributed to donor-specific HLA antibodies (DSA) [6–11], the diagnosis of AMR depends on input from multiple transplant professionals. Starting from clinical suspicion, with input from immunologists, who verify the presence of current and/or historic DSA, and pathologists, who assign pertinent lesion scores (e.g., C4d, glomerulitis and peritubular capillaritis) and verify the presence of additional diagnostic features, AMR is classified into active, chronic-active, or chronic subtypes. Once diagnosed, transplant professionals rely on the activity and chronicity observed on allograft biopsies to inform future maintenance immunosuppression regimens and supplemental therapies for AMR (e.g., to decrease the production or increase the elimination of DSA, inhibit complement, or other targeted therapies), as well as the preferred monitoring schedule.

A prior survey by the Banff Antibody-Mediated Injury Workgroup found that the diagnosis of AMR was vulnerable to misinterpretation, and this was attributed, among others, to the fact that the diagnostic features of AMR, such as DSA information, were not available at the time of biopsy review. The survey also established that non-HLA antibodies and/or molecular transcripts were primarily obtained when AMR histological features were present, but DSA was not detected [12]. Decisions made by multidisciplinary teams have been shown to be more likely to align with guidelines than those made independently by individual clinicians [1, 13, 14]. Whether bringing together the various transplant professionals involved in the diagnosis of AMR in multidisciplinary meetings may improve communication with laboratory-based transplant professionals and facilitate standardized application of diagnostic tools, as well as harmonize the diagnosis and management of AMR in clinical practice, is unknown.

In this manuscript, we provide the findings of an international survey on contemporary global practices of multidisciplinary meetings that simultaneously bring together the perspectives of various professionals involved in the care of transplant patients; conduct comparative analysis on these practices within high-income (i.e., North America, Europe, and Australia/Oceania) versus low-to-middle-income (Central/South America, Africa, and Asia) regions and by center size; as well as inquire about their perceived value and the barriers to their implementation. This manuscript represents an initial step toward standardization of approaches to the provision of patient care across the world. As such, while providing insights on how to facilitate multidisciplinary meetings, it leaves to future research to inquire into and elucidate the potential reasons for any disparities across national boundaries and practical solutions to overcome such hurdles for the achievement of standardization of diagnoses and harmonization of care.

2 | Materials and Methods

2.1 | Participants and Methods

2.1.1 | Study Design

In this cross-sectional study, the Banff Antibody-Mediated Injury Working Group conducted a survey on multidisciplinary post-transplant meetings by distributing it among members of various professional societies (e.g., histocompatibility, pathology, and transplantation).

2.1.2 | Study Preparation, Data Collection Methods, and Respondent Characteristics

The survey questionnaire included 35 questions (see Supporting Information 1), seeking information on the respondents (e.g., clinical role, organ-specific expertise, and institutional affiliations) and centers of practice (e.g., location, size, practice type, and affiliation). The survey further sought to verify the availability of multidisciplinary meetings, their content and conduct when available (e.g., participants, frequency, organs discussed, and mode of participation). Another section of the survey focused on AMR case presentations (e.g., number of cases, information presented [i.e., clinical and social data], diagnostic tests, expertise of participants, and outcomes of these meetings [e.g., management decisions]). Finally, the survey sought to establish the perceived value of multidisciplinary meetings and barriers to their implementation. The survey was pre-tested by members of the working group providing clinical, immunology, and pathology perspectives. The final version of the survey was implemented in REDCap, a secure web application for building and managing online surveys and databases.

Seeking to gain insight on global perspectives, members of the Banff Antibody-Mediated Injury Working Group approached organ specific (International Society of Nephrology (ISN), ERA-EDTA Descartes, Sociedad Latinoamericana de Nefrología e Hipertensión (SLANH)); transplantation (American Society of Transplantation (AST) and Transplant Surgeons (ASTS), the Transplantation Society (TTS), European Kidney Transplant Association (EKITA), The European Society for Organ Transplantation (ESOT), Transplantation Society of Australia & New Zealand (TSANZ), African Society of Organ Transplantation (ASOT), Asian Society of Transplantation, Sociedad de Trasplantes de América Latina y el Caribe (STALYC), Brazilian Transplantation Society (ABTO), Canadian Society of Transplantation (CST), Egyptian Society of Transplantation, Indian Society of Transplantation, Italian Society for Organs and Tissues Transplantation (SITO), Middle Eastern Society of Organ Transplantation (MESOT)); histocompatibility and immunogenetics (American Society of Histocompatibility and Immunogenetics (ASHI), Latin American Histocompatibility & Immunogenetics society); and pathology (Renal Pathology Society and Sociedad Latinoamericana de Patología (SLAP)) societies to distribute the survey. Data from consecutive members of the approached societies who responded to the survey and completed key queries describing their role on the transplant team were included.

2.1.3 | Survey Administration

Links to the web-based REDCap survey were distributed by the organizations to their members by email (e.g., CST), as newsletters (e.g., TTS), and in community of practice communications (e.g., AST, ASTS). The survey opened on October 9, 2023, and closed on April 15, 2024. To maximize outreach as well as promote participation and maximize generalizability, the organizations distributing the survey were requested to send three reminders at 2-week intervals. Follow-up e-mails were sent to the distributing organization to ensure repeated survey distribution. Organizations complied with this procedure to the best of their ability, given their individual policies on approaching their membership. To ensure respondents participated in our web-based survey only once and avoid “multiple participation,” the communication accompanying the survey link alerted potential participants to refrain from completing the survey again, had they previously completed it when distributed by another organization.

2.1.4 | Ethical Considerations

The Yale University Institutional Review Board approved this study protocol. Respondents' consent to participate was inferred from their responding to survey questions. No personal or center-level identifying information was considered in the analysis to ensure participant confidentiality and anonymity.

2.1.5 | Statistical Analysis

Data management and statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC). Distributions of respondent and center characteristics alongside those pertaining to the various survey domains (multidisciplinary meeting characteristics, AMR discussions, perceived value, and barriers to implementation) were described for continuous and categorical variables using descriptive statistics as appropriate. The proportions of missing data are reported for each survey question when relevant. The chi-square test was used to assess differences across high- and low-to-middle-income regions as well as by center size. A two-sided p value < 0.05 was considered of statistical significance. Figures were generated using Biorender (Science Suite Inc. Toronto, Ontario, Canada) and GraphPad Prism version 9.3.1 for MacOS (GraphPad Software, San Diego, CA). We followed the CROSS Checklist for Reporting of Survey Studies [15].

3 | Results

3.1 | Characteristics of Survey Respondents and Transplant Centers

Of the 574 respondents who accessed the survey, 172 did not complete the introductory survey questions and were, thus, excluded. A detailed study flow diagram can be found in Supporting Information 2.

A total of 402 respondents, arising from 330 institutions worldwide, completed the survey. Respondents and center characteristics are presented in Supporting Information 3. Of the

possible disciplines, we observed the greatest participation among internists specializing in transplantation, surgeons, pathologists, and immunologists/HLA experts. The respondents were engaged in the care of kidney (90.55%), liver (21.14%), pancreas (20.65%), heart (15.17%), and lung (14.18%) transplant recipients. Most respondents (87.06%) practiced at a single university-affiliated academic center. Transplant centers were in North America (44.53%), followed by Asia (23.88%), Europe (16.92%), Central/South America (11.19%), Australia/Oceania (1.99%), and Africa (1.49%).

Of the 402 survey respondents, 302 respondents (75.12%) indicated that their institutions conducted multidisciplinary meetings that reviewed post-transplant care and were attended primarily by internists specializing in transplantation, as well as surgeons, nurses, pathologists, immunologists, and pharmacists. Of the remaining respondents, 98 (24.38%) indicated that their institutions did not conduct multidisciplinary meetings, and the responses of 2 (0.50%) survey respondents were missing. Table 1 presents respondent and center characteristics across centers practicing multidisciplinary meetings versus not.

3.2 | Global Practices of Multidisciplinary Meetings

Multidisciplinary meetings were more prevalent in academic centers from North America, Europe, and Australia/Oceania in comparison to Asia, Central/South America, and Africa (81.03% vs. 65.99%; $p < 0.001$). Also, multidisciplinary meetings were more prevalent in mid- to large-size transplant programs (56.52%, 77.61%, and 86.71% for centers performing <50, 51–150, >150 transplants annually, respectively; $p < 0.001$, see Supporting Information 4).

Transplant professionals from high-income regions were more likely than low-income regions to attend meetings remotely (e.g., video conferencing: 40.49% vs. 10.31%, $p < 0.001$) or through a combination of in-person and remote participation (55.12% vs. 41.24%, $p = 0.024$). Meanwhile, high-income regions were less likely to attend meetings solely in person compared to low-income regions (19.51% vs. 52.58%, $p < 0.001$). Similarly, meetings were more likely to be attended in person rather than remotely or as Hybrid meetings in smaller centers in comparison to larger centers (see Supporting Information 5).

There was no statistically significant difference by region or center size in the type of transplant professionals attending multidisciplinary meetings, except for pharmacists, who were more likely to attend these meetings in high-income versus low-income regions (43.41% vs. 27.84%, respectively; $p = 0.009$) and in larger centers. Also, transplant immunologists were more likely to attend meetings in larger transplant centers (see Supporting Information 6).

When reporting on the frequency of the multidisciplinary meetings, half of the respondents indicated they occur at least weekly, while a third reported they occur monthly (Supporting Information 7). A higher frequency of meetings was reported the larger the transplant center (meetings occurring at least weekly in 23.08%, 56.73%, and 61.48% of respondents practicing at

centers conducting <50, 51–150, and >150 transplants annually, respectively). Similarly, meetings occur more frequently in high-income versus low-to-middle-income regions (60.10% vs. 37.11% for meetings occurring at least weekly; $p < 0.001$, Supporting Information 8).

3.3 | Perceived Value and Barriers to Conducting Multidisciplinary Meetings

Respondents, who had access to multidisciplinary meetings, reported the meetings allowed for continued professional development (97.68%) and had didactic value with content geared toward trainees (95.70%, Supporting Information 7). Respondents, who reported that multidisciplinary meetings were not conducted at their institutions ($N = 98$), proposed the unavailability of transplant professionals to attend meetings (63.27%), another reason (not otherwise identified, 30.61%), lack of support for remote participation (17.35%), or unavailability of space to conduct meetings (4.08%) as possible causes. Importantly, only a minority of the respondents who did not have access to multidisciplinary meetings indicated that they saw no need for multidisciplinary meetings (5.10%).

3.4 | AMR Case Presentations in Multidisciplinary Meetings

Of the 302 respondents practicing at centers that subscribed to multidisciplinary meetings, most ($N = 217$, 71.85%) confirmed that AMR was discussed in these meetings, a minority (26.82%) indicated that their institutions did not discuss AMR, and four respondents did not provide an answer (1.32%). Transplant professionals were often onsite, with only a minority practicing offsite (e.g., transplant immunologists/HLA experts) and contributing to decision-making remotely and/or outside of the meetings (Supporting Information 9). Of the 217 respondents engaging in AMR case presentations, the majority indicated that the presentations included review of clinical information (i.e., patient characteristics, organ function, non-adherence, proteinuria, etc. [98.16%]), maintenance immunosuppression and/or treatment for rejection (93.09%), HLA antibody assays (77.42%), and histological findings (81.57%). Additionally, 46.08% of AMR case presentations discussed patients' socioeconomic context, and a third reviewed non-HLA/pathogenic autoantibody results and molecular assays (Supporting Information 9).

When comparing regional practices, we found that while there were no striking differences by center size or region with regards to the content of AMR case presentations, molecular assays, such as dd-cfDNA, MMDx, and Nanostring, were more frequently used in high-income compared to low-to-middle-income regions (46.71% and 12.31%, respectively; $p < 0.001$).

Over 90% of the respondents indicated that AMR case presentations resulted in actionable management plans (Supporting Information 9). Most respondents participating in multidisciplinary meetings reported that AMR case presentations were valuable for informing patient care (Table 2) and thought that patient characteristics, pathology, and histocompatibility should be routinely discussed when reviewing and fine-tuning AMR

TABLE 1 | Respondent and center characteristics across centers practicing multidisciplinary meetings versus not.

	Yes (N = 302)	No (N = 98)	Total number of respondents (N = 400)^b
Respondents' clinical role^a			
Transplant physician ^c	113 (37.42%)	39 (39.80%)	152 (38.00%)
Transplant surgeon	52 (17.22%)	10 (10.20%)	62 (15.50%)
Pharmacist	10 (3.31%)	1 (1.02%)	11 (2.75%)
Pathologist	92 (30.46%)	32 (32.65%)	124 (31.00%)
Immunologists/HLA expert	43 (14.24%)	13 (13.27%)	56 (14.00%)
Nurse coordinator/practitioner	3 (0.99%)	7 (7.14%)	10 (2.50%)
Respondents' solid organ of focus^a			
Kidney	273 (90.40%)	89 (90.82%)	362 (90.50%)
Heart	47 (15.56%)	13 (13.27%)	60 (15.00%)
Liver	73 (24.17%)	12 (12.24%)	85 (21.25%)
Lung	41 (13.58%)	15 (15.31%)	56 (14.00%)
Uterus/VCA	5 (1.66%)	0 (0.00%)	5 (1.25%)
Pancreas	72 (23.84%)	11 (11.22%)	83 (20.75%)
Islets of pancreas	16 (5.30%)	1 (1.02%)	17 (4.25%)
Other	7 (2.32%)	3 (3.06%)	10 (2.50%)
Respondents practicing at a single center			
Yes	266 (88.08%)	82 (83.67%)	348 (87.00%)
No	35 (11.59%)	16 (16.33%)	51 (12.75%)
Missing	1 (0.33%)	0 (0.00%)	1 (0.25%)
Practice location			
North America	142 (47.02%)	35 (35.71%)	177 (44.25%)
Europe	55 (18.21%)	13 (13.27%)	68 (17.00%)
Central/South America	26 (8.61%)	19 (19.39%)	45 (11.25%)
Asia	67 (22.19%)	29 (29.59%)	96 (24.00%)
Africa	4 (1.32%)	2 (2.04%)	6 (1.50%)
Australia/Oceania	8 (2.65%)	0 (0.00%)	8 (2.00%)
Total number of solid organ transplants performed per year			
<50	52 (17.22%)	40 (40.82%)	92 (23.00%)
51–100	63 (20.86%)	18 (18.37%)	81 (20.25%)
101–150	41 (13.58%)	12 (12.24%)	53 (13.25%)
151–200	39 (12.91%)	4 (4.08%)	43 (10.75%)
>200	98 (32.45%)	17 (17.35%)	115 (28.75%)
I am not sure	9 (2.98%)	7 (7.14%)	16 (4.00%)
Practice affiliation			
Academic center only	196 (64.90%)	56 (57.14%)	252 (63.00%)
Academic and private practice	53 (17.55%)	20 (20.41%)	73 (18.25%)
Non-academic private practice only	20 (6.62%)	8 (8.16%)	28 (7.00%)
Non-academic public practice (NHS)	36 (11.92%)	13 (13.27%)	49 (12.25%)
Other	9 (2.98%)	5 (5.10%)	14 (3.50%)

Abbreviation: VCA, vascularized composite allotransplant.

^aRespondents were able to select one or more answers to this query.^bA response to the question on whether multidisciplinary meetings were conducted was missing for two of the 402 survey respondents.^cTransplant physicians represent internists specializing in transplantation.

TABLE 2 | Perceived value of AMR discussions, preferred format, and content among respondents attending multidisciplinary meetings that discuss AMR vs. not.

	AMR discussed (N = 217)	AMR not discussed (N = 81)	Total number of respondents (N = 298) ^b
AMR case discussions during multidisciplinary meetings improve patient care			
Yes	216 (99.54%)	76 (93.83%)	292 (97.99%)
No	0 (0.00%)	4 (4.94%)	4 (1.34%)
Missing	1 (0.46%)	1 (1.23%)	2 (0.67%)
Matters pertaining to AMR diagnosis that should be discussed during multidisciplinary meetings ^a			
Histological biopsy slides	189 (87.10%)	73 (90.12%)	262 (87.92%)
HLA antibody assay results (HLA Donor-specific antibodies (DSA)	194 (89.40%)	71 (87.65%)	265 (88.93%)
Non-HLA antibody assay results	149 (68.66%)	45 (55.56%)	194 (65.10%)
Donor-derived cell free DNA (dd-cfDNA)	128 (58.99%)	44 (54.32%)	172 (57.72%)
Molecular microscope (MMDx)	97 (44.70%)	31 (38.27%)	128 (42.95%)
Nanostring	61 (28.11%)	15 (18.52%)	76 (25.50%)
Clinical information (patient characteristics, organ function, non-adherence, proteinuria, etc.)	174 (80.18%)	70 (86.42%)	244 (81.88%)
AMR diagnosis made by pathologists should be (re)assigned by consensus during or after multidisciplinary meetings			
No	68 (31.34%)	18 (22.22%)	86 (28.86%)
Yes	146 (67.28%)	62 (76.54%)	208 (69.80%)
Missing	3 (1.38%)	1 (1.23%)	4 (1.34%)
Matters pertaining to AMR management that should be discussed during multidisciplinary meetings ^a			
Revisions of immunosuppression regimen	192 (88.48%)	68 (83.95%)	260 (87.25%)
Establish a consensus on supplemental AMR treatment	177 (81.57%)	60 (74.07%)	237 (79.53%)
Review pharmacogenomics (PGx) testing results	73 (33.64%)	24 (29.63%)	97 (32.55%)
Establish consensus on monitoring (e.g., follow-up biopsy or antibody monitoring)	174 (80.18%)	68 (83.95%)	242 (81.21%)
Discuss follow-up and outcomes of AMR cases	192 (88.48%)	71 (87.65%)	263 (88.26%)
Multidisciplinary transplant meetings improve patient care			
No	2 (0.92%)	1 (1.23%)	3 (1.01%)
Yes	211 (97.24%)	78 (96.30%)	289 (96.98%)
Missing	4 (1.84%)	2 (2.47%)	6 (2.01%)

Abbreviations: AMR, antibody-mediated rejection; DSA, donor-specific antibodies; IS, immunosuppression; PGx, pharmacogenomics.

^a Respondents were able to select one or more answers to this query.

^b A response to the question on whether AMR was discussed in multidisciplinary meetings was missing for four of the 302 survey respondents practicing at centers with multidisciplinary meetings.

diagnoses (Figure 1A). Also, non-HLA/pathogenic autoantibody results (68.66%), donor-derived cell free DNA (dd-cfDNA, 58.99%), molecular microscope (MMDx, 44.70%), and Nanostring (28.11%) results were also deemed desirable when discussing AMR (Figure 1B). These diagnostic tests were deemed similarly desirable across regions except for molecular diagnostics, including dd-cfDNA (63.82% vs. 47.69%; $p = 0.027$) and MMDx (50.66% vs. 30.77%; $p = 0.007$), which were more frequently noted

to be of interest among respondents from high-income compared to low-to-middle-income regions, respectively.

When inquiring about matters pertaining to AMR diagnosis that should be discussed during multidisciplinary meetings, there was wide agreement among respondents that multidisciplinary meetings should promote revisions of AMR management plans (i.e., therapy and monitoring), and be a venue for reporting

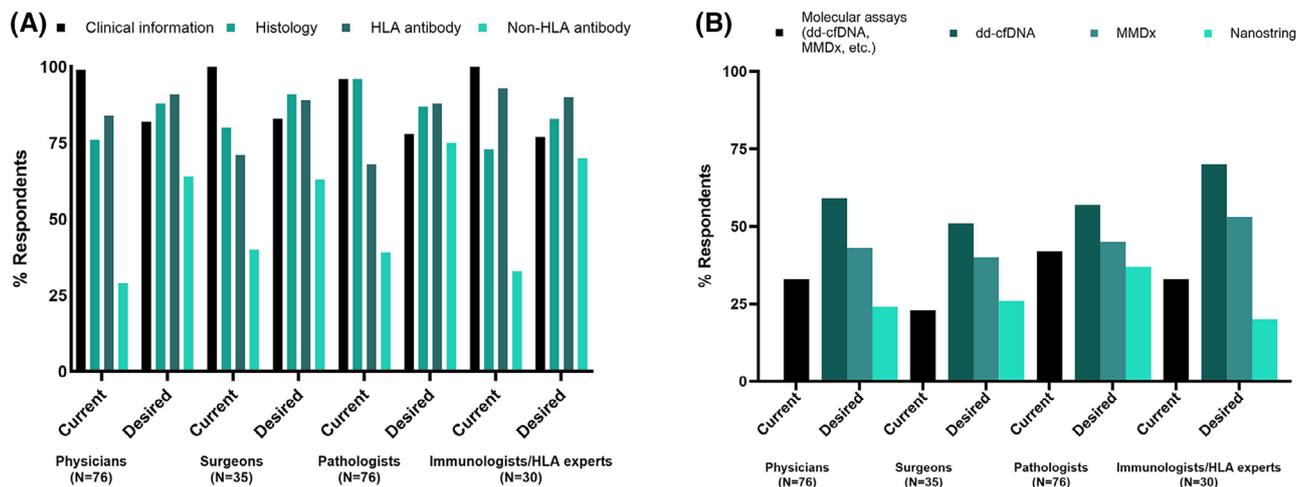


FIGURE 1 | Diagnostic tools for AMR currently discussed and those deemed desirable to discuss in future multidisciplinary meetings by respondents' role. (A) Current practices and future preferences related to clinical information (e.g., patient characteristics, organ function, non-adherence, and proteinuria), histology, HLA antibody assays, and non-HLA antibody assays. (B) Current practices and future preferences related to molecular assays (i.e., donor-derived cell free DNA, molecular microscope, and Nanostring) by the clinical role of survey respondents. Each figure presents the percentage of respondents, from the overall number of respondents performing the clinical role, who confirmed that a diagnostic tool is currently used and those indicating a diagnostic tool would be desired. *Several respondents indicated they had more than one clinical role within the multidisciplinary team (e.g., transplant internist/surgeon and immunologist), and, thus, their responses would be captured in multiple columns. Transplant physicians represent internists specializing in transplantation. **Given the small number of respondents, distributions of answers provided by several transplant professionals (e.g., nurses and pharmacists) are not presented in this figure. □ Transplant physicians refer to internists specializing in transplantation. dd-cfDNA, donor-derived cell free DNA; MMDx, molecular microscope.

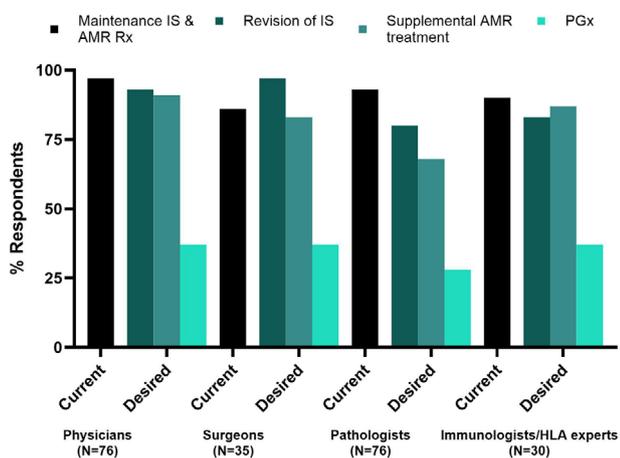


FIGURE 2 | AMR management aspects currently discussed and those deemed desirable to discuss in future multidisciplinary meetings by respondents' role. *Several respondents indicated they had more than one clinical role within the multidisciplinary team (e.g., transplant internist/surgeon and immunologist), and, thus, their responses would be captured in multiple columns. Transplant physicians represent internists specializing in transplantation. **Given the small number of respondents, distributions of answers provided by several transplant professionals (e.g., nurses and pharmacists) are not presented in this figure. □ Transplant physicians refer to internists specializing in transplantation. AMR, antibody-mediated rejection; IS, immunosuppression; PGx, pharmacogenomics; Rx, treatment.

and reflecting on implications of the therapies administered to long-term outcomes (Table 2). Current and desired management-related topics for discussion at multidisciplinary meetings are presented in Figure 2. Most of the 217 respondents from cen-

ters in which multidisciplinary meetings discussed AMR, felt that these discussions could benefit patient care (99.54%), and found that histopathology (87.10%), clinical information (80.18%), and anti-HLA antibody (89.40%) data were most important to review (Table 2). More than half of the respondents found that reviewing non-HLA/pathogenic autoantibodies (68.66%) and dd-cfDNA (58.99%), and less so, the results of biopsy-based transcript diagnostics (i.e., MMDx and Nanostring), during AMR case presentations would be desirable. There was wide agreement on the role of multidisciplinary meetings in facilitating decisions on maintenance immunosuppression, supplemental therapies for AMR, as well as long-term laboratory and clinical surveillance (Table 2) with management decisions primarily relying on input from internists (90.32%), surgeons (48.85%), and to a lesser extent from transplant pathologists, immunologists and pharmacists.

4 | Discussion

Our survey on global practices of multidisciplinary meetings in clinical transplantation, and particularly in relation to AMR, established that these meetings were more prevalent in high-income compared to low-to-middle-income regions and were conducted more frequently at mid- to large-size transplant programs in which, in addition to internists, surgeons, and pathologists, laboratory-based transplant immunologists/HLA experts were present onsite, and pharmacists also frequented the multidisciplinary meetings. While histology, anti-HLA antibodies, and clinical characteristics were considered in most AMR case presentations, molecular diagnostics, including dd-cfDNA and MMDx, were more frequently noted to be of interest among respondents from high-income compared to low-to-

middle-income regions. Whether they were already engaged in discussions on AMR cases during multidisciplinary meetings or not, most respondents felt that such discussions would be valuable for improving clinical care, allowing finalization of AMR diagnoses and management decisions. Most respondents also found that these meetings promoted continued professional development and trainee education.

Multidisciplinary care is necessary for addressing the various health concerns experienced by patients with end-stage organ disease [16–18]. Of the health concerns experienced by transplant patients, AMR represents an important diagnostic and therapeutic challenge [19, 20]. Classifications of active, chronic active, and chronic AMR rely on input from pathologists and HLA experts [6]. Despite efforts to standardize the application of the Banff classification, evidence suggests that these diagnoses are vulnerable to misclassification [21]. Based on an examination of international practices for diagnosing AMR, one explanation may be the unavailability of DSA data at the time of histology review [12]. Our survey established the valuable role laboratory-based experts play in the verification of immune-mediated injuries. As the transplantation community strives to ensure standardized laboratory procedures, interpretation, and reporting, there is a reliance on input from HLA experts to interpret complex HLA antibody data. Given the growing appreciation of immune injury related to DSA, even in organs not previously considered vulnerable [22], for timely diagnosis and initiation of therapy for AMR, whenever possible, transplant centers are encouraged to simultaneously order pathology and DSA and advocate for rapid turnaround time. Inevitably, disparities in access to HLA experts, as observed in small- compared to mid- and large-size transplant programs, in which HLA experts are less likely to practice onsite and/or attend multidisciplinary meetings, might contribute to challenges in timely access to DSA data and standardized AMR diagnosis in day-to-day clinical practice. When participation of pertinent experts in multidisciplinary meetings may not always be possible, effectively written reports and interpretation of assay results (e.g., communication of unambiguously negative DSA results) may serve as acceptable substitutes for in-person/virtual participation. Yet, it is important to emphasize that multidisciplinary meetings represent a unique opportunity to bring together the various transplant professionals involved in the diagnosis of AMR, to capture the presence or absence of the relevant diagnostic criteria, and assign the AMR diagnosis according to the most recent Banff classification, while acknowledging uncertainty related to each of the diagnostic criteria, highlighting pertinent differential diagnosis other than AMR, and confirming consensus as to the assigned diagnosis.

Interestingly, our survey established that there was a rather wide uptake of some of the less standardized diagnostic tools [6, 23], with approximately a third of respondents indicating an interest in discussing non-HLA antibody assays and molecular diagnostics at multidisciplinary meetings. Our survey could not establish the frequency of implementation of these diagnostic tools in clinical practice but shows that molecular diagnostics, including dd-cfDNA and MMDx, are more frequently deemed to be of interest among respondents from high- compared to low-middle-income regions. As new diagnostic tools are being promoted for inclusion in the Banff classification, with various

degrees of evidence as to their clinical utility above and beyond the existing Banff lesion scores and additional diagnostic features, multidisciplinary meetings may be well poised to promote discussion on and carefully consider the utilization of emerging diagnostic tools, establish consensus on their adoption, and inform local policies for their standardized application in clinical practice. Similarly, multidisciplinary meetings could be used to solicit future participation in rigorously designed pragmatic international interventional and observational studies as the transplantation community seeks to bolster sufficient power to evaluate emerging biomarkers and therapies.

AMR diagnoses must be standardized to overcome the equipoise related to the effectiveness of therapies targeting antibody production [19, 20], and this is more likely to be accomplished with multidisciplinary input. Efforts to eliminate DSA may require close collaboration with other professionals (e.g., hematologists overseeing plasmapheresis). Multidisciplinary input may be particularly beneficial when dealing with uncertainty in terms of the best course of action in the absence of high-quality evidence and when considering the implications of supplemental therapy on future immunosuppression complications [1]. Importantly, efforts to personalize care, minimize drug interactions and toxicity require input from pharmacists and pharmacologists [24]. Our survey, however, finds that pharmacists do not readily attend multidisciplinary meetings, and this gap is more pronounced in low-to-middle-income regions. Management considerations related to potential long-term infectious, oncologic, metabolic, and cardiovascular complications of immunosuppression may also benefit from multidisciplinary discussions involving infectious disease specialists, oncologists, endocrinologists, cardiologists, and intensivists, eventually improving outcomes and experiences of transplant patients along their post-transplant journey. Psychologists and social workers also have a role in addressing patients' socioeconomic circumstances, health literacy, self-management, preferences and values [25–28], all of which affect adherence and access to health services.

Our survey benefits from global participation and input from diverse perspectives of transplant professionals represented in care teams arising from centers of diverse sizes and practice types, including those with and without multidisciplinary meetings. Despite these advantages, limitations must be noted. First, our study observations depend on the perspectives of the respondents participating, based on their role, center characteristics, and the regions they arose from. Second, while respondents indicated that pathologist-assigned diagnoses may be revised at multidisciplinary meetings, the survey did not prompt the respondents to indicate based on what information and in what way the diagnoses were revised (e.g., availability of DSA, histology, activity vs. chronicity, presence vs. absence of AMR). The survey also did not establish how the revised diagnoses were reported in the medical record and conveyed to patients, or what follow-up investigations (e.g., repeat biopsies, antibody testing, or molecular diagnostics), monitoring schedule, and interventions, were applied thereafter. Finally, like other surveys, our study may be vulnerable to response bias, resulting in an inflated perceived value of multidisciplinary meetings. It is important to note, however, that while survey respondents who regularly

TABLE 3 | Recommendations for leveraging multidisciplinary meetings for standardized diagnosis and harmonized management of antibody-mediated rejection.*

1. Secure pre-scheduled multidisciplinary meetings.
 2. Conduct meetings at regular intervals, with the frequency of meetings informed by the number of transplants conducted at the center, number of AMR cases for discussion, and urgency of decision making. (Mid-to-large-size centers conduct meetings at least weekly).
 3. Facilitate participation by securing a physical location or, for those who cannot attend in person, a confidential virtual meeting platform.
 4. Incentivize participation in multidisciplinary meetings through protected time, remuneration, and/or continued medical education credits.
 5. Engage medical, surgical, and laboratory-based trainees to participate in case presentations at multidisciplinary meetings.
 6. Ensure the following members of the multidisciplinary team are in attendance when diagnosing AMR:
 - a. Transplant internists and surgeons: to provide clinical information, gauge immunological risk, provide background information on adherence to immunosuppression, and inform on risks related to augmentation of immunosuppression.
 - b. Pathologists: to review histology in consideration of the most recent Banff classification.
 - c. Transplant immunologists: to review HLA (in)compatibility, memory response, and anti-HLA donor specific antibody assay results in consideration of the most recent STAR recommendations.
 7. Carefully consider the quality of evidence and clinical utility of additional diagnostic tools (e.g., non-HLA/pathogenic autoantibodies and/or molecular diagnostics) in supporting or excluding AMR diagnosis.
 8. The leader of the case presentation will assign the AMR diagnosis according to the most recent Banff classification while:
 - a. acknowledging uncertainty related to each of the diagnostic criteria,
 - b. highlighting pertinent differential diagnosis other than AMR; and
 - c. confirming consensus as to the final assigned diagnosis.
 9. The multidisciplinary team will discuss relevant interventions while considering activity and chronicity of AMR as well as patient-specific risk factors for adverse events related to supplemental immunosuppression:
 - a. invite input from additional professionals (e.g., pharmacists, social workers, psychologists, infectious disease experts, oncologists) depending on patient-level risk factors; and
 - b. discuss uncertainties related to the effectiveness of interventions.
 10. The leader of the case presentation will summarize the preferred therapeutic and monitoring schedule given the patients' immunological risk, diagnosis, and potential risks associated with therapy and will confirm consensus on the management plan.
 11. The leader of the case presentation will confirm the interval at which a follow-up report will be provided to the multidisciplinary team on the patient's adherence to the recommended therapeutic plan and outcome.
 12. The treating transplant team will report back regularly to the multidisciplinary team on patient outcomes following the interventions and monitoring schedule agreed upon with the patient to reflect on the effectiveness of the implemented therapeutic plan, as well as potential disparities in care.
- *Supplemental steps toward enhanced patient-centered care:
1. The treating transplant team will inform patients undergoing work up for AMR that their case may be presented at multidisciplinary meetings to accomplish consensus on the diagnosis and management.
 2. The treating transplant team will report the conclusions of multidisciplinary meetings to the transplant recipient while sharing uncertainties/differential diagnosis, monitoring recommendations, and prognosis transparently, whenever possible; discuss the need for supplemental therapy, effectiveness, potential adverse effects, and alternatives; and partner with transplant patients in adjusting the therapeutic plan outlined in the multidisciplinary meeting in alignment with the patient's preferences and values.

attended multidisciplinary meetings and discussed AMR were inclined toward conducting them, a similarly high proportion of respondents who did not routinely discuss AMR during multidisciplinary meetings also perceived these meetings to be of value.

5 | Conclusion

Our survey showed that multidisciplinary meetings are essential for AMR diagnosis and patient care and can foster collaboration among different transplant professionals. Barriers to the

implementation of multidisciplinary meetings primarily relate to a lack of pertinent expertise onsite. Centers engaged with transplant immunologists and/or pathologists who are based offsite are less likely to conduct multidisciplinary meetings. Table 3 provides an overview of recommendations on engaging in multidisciplinary meetings for standardized diagnosis and harmonized management of AMR and strategies to overcome regional and center size-related disparities identified by our survey. Remote participation and/or web-based consultation with expert panels may be a means to overcome these gaps. The provision of continued medical education credits, protected time, or remuneration for attending or educating trainees during multidisciplinary meetings may also promote participation. Similarly, securing transplant professionals' time to attend these meetings, as well as a physical location or, for those who cannot attend in person, a confidential virtual meeting platform, are also likely enablers. Carefully curated educational resources of updated diagnostic schemes and decision support tools for AMR management may serve as valuable supplements or temporary alternatives to multidisciplinary meetings in smaller centers and low-to-middle income countries. Finally, future studies are needed to outline post-implementation evaluation of the clinical impact of multidisciplinary meetings. In the interim, periodic responses to a collection of queries on whether the diagnosis was correctly applied, the appropriateness of treatment implemented, and whether a satisfactory response was observed to treatment are likely to ensure that multidisciplinary meetings facilitate the delivery of high-value AMR care.

6 | Practitioner Points

1. Diagnosis of antibody-mediated rejection (AMR) is vulnerable to misinterpretation, and its diagnostic criteria are not readily and simultaneously available. There is a need to standardize AMR diagnoses and harmonize its management across borders.
2. Multidisciplinary meetings can facilitate communication between transplant professionals, and decisions made by multidisciplinary teams are more likely to align with guidelines than those made by clinicians independently. Yet, there are disparities in the conduct of multidisciplinary meetings and in access to transplant professionals like transplant immunologists in high- compared to low-income regions and by center size.
3. Facilitating multidisciplinary meetings by reserving a physical location, using a confidential virtual meeting platform, securing transplant professionals' time to attend the meeting, and incentivizing participation in multidisciplinary meetings through remuneration, protected time, and/or continued medical education credits, may increase the adoption of multidisciplinary meetings, and consequently, help standardize AMR diagnoses and harmonize its management globally.

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Conflicts of Interest

The authors of the manuscript have no conflict of interest to declare.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.