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Meeting Report

Banff 2013 Meeting Report: Inclusion of C4d-Negative Antibody-Mediated Rejection and Antibody-Associated Arterial Lesions

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The 12th Banff Conference on Allograft Pathology was held in Comandatuba, Brazil, from August 19–23, 2013, and was preceded by a 2-day Latin American Symposium on Transplant Immunobiology and Immunopathology. The meeting was highlighted by the presentation of the findings of several working groups formed at the 2009 and 2011 Banff meetings to: (1) establish consensus criteria for diagnosing antibody-mediated rejection (ABMR) in the presence and absence of detectable C4d deposition; (2) develop consensus definitions and thresholds for glomerulitis (g score) and chronic glomerulopathy (cg score), associated with improved inter-observer agreement and correlation with clinical, molecular and serological data; (3) determine whether isolated lesions of intimal arteritis (''isolated v'') represent acute rejection similar to intimal arteritis in the presence of tubulointerstitial inflammation; (4) compare different methodologies for evaluating interstitial fibrosis and for performing/evaluating implantation biopsies of renal allografts with regard to reproducibility and prediction of subsequent graft function; and (5) define clinically and prognostically significant morphologic criteria for subclassifying polyoma virus nephropathy. The key outcome of the 2013 conference is defining criteria for diagnosis of C4d-negative ABMR and respective modification of the Banff classification. In addition, three new Banff Working Groups were initiated.

Keywords: Acute allograft rejection, antibody-mediated rejection, Banff schema, cardiac allograft, chronic allograft rejection, complement C4d, composite tissue allograft, donor-specific antibodies, liver allograft, lung transplantation, pancreas allograft, renal transplantation, transplant biopsy, transplant glomerulopathy, transplant pathology

Abbreviations: ABMR, antibody-mediated rejection; ADCC, antibody-dependent cellular cytotoxicity;

BIFQUIT, Banff initiative for quality assurance in transplantation; BWG, Banff Working Group; CAV, cardiac allograft vasculopathy; CD, cluster of differentiation; DeKAF, long-term deterioration of kidney allograft function; DSAs, donor-specific antibodies; DSAST, donor-specific antibody-selective gene transcript; EM, electron microscopy; ENDAT, endothelial activation and injury transcript; FOXP3, forkhead box P3; GBM, glomerular basement membrane; HLA, human leukocyte antigen (major histocompatibility complex); IF, immunofluorescence; IF/TA, interstitial fibrosis and tubular atrophy; IgG, immunoglobulin G; IL, interleukin; IP, immunoperoxidase; ISHLT, International Society for Heart & Lung Transplantation; KOL, key opinion leader; MVI, microvascular injury; NKOL, new key opinion leader; pAMR, pathologic antibody-mediated rejection (heart allografts); PAS, periodic acid-Schiff; TCMR, T cell–mediated rejection; TG, transplant glomerulopathy; VCA, vascularized composite allograft

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Introduction

The 12th Banff Conference on Allograft Pathology was held in Comandatuba, Brazil, from August 19–23, 2013, and was attended by 222 transplant pathologists, clinicians, surgeons, immunologists and researchers from five continents. A major focus of the conference was the presentation of findings of organ-specific Banff Working Groups (BWGs) initially formed at the 2009 and 2011 Banff meetings. These findings have resulted in new or modified criteria and specific recommendations for the diagnosis and reporting of a number of lesions, including but not limited to antibody-mediated rejection (ABMR) and T cell–mediated rejection (TCMR) in renal and other solid organ allografts. The conference was preceded by a 2-day Latin American Symposium on Transplant Immunobiology and Immunopathology, sponsored by the Brazilian Association for Organ Transplantation and the Transplantation Society.

Summary of the Latin American Symposium on Transplant Immunobiology and Immunopathology

The symposium was designed to emphasize work in these areas being done in the Latin American community and promote interaction between Latin American and international transplant centers. Four sessions were moderated by invited guests (Appendix). Twenty abstracts submitted by Latin American investigators were presented by junior, new key opinion leaders (NKOLs) and discussed by their respective senior mentors (key opinion leaders [KOLs]), session moderators and the audience.

In the immunobiology sessions, the main subjects were adipokines in graft rejection and tolerance, association of soluble CD30 levels with protocol biopsy findings, C1q-fixing properties and IgG subclasses of anti-HLA antibodies, and the role of HLA-G genotypes and plasma levels of soluble HLA-G in posttransplant evaluation. In addition, the impact of ABMR in kidney and heart transplantation and the utility of testing for donor-specific antibodies (DSAs) in determining immunosuppressive therapy and monitoring desensitization were examined.

In the immunopathology sessions, topics included staining of heart and kidney allograft biopsies for forkhead box P3 (FOXP3), IL-17 and CD68, the impact of preimplantation biopsies, protocol biopsies in sensitized patients, the clinical impact of C4d positivity in renal allograft biopsies, lymphangiogenesis in renal allografts, comparisons between findings in kidney and pancreas biopsies in simultaneous kidney–pancreas allograft recipients, and comparing microarray-based ABMR scores with histology, C4d and DSA in predicting graft survival.

This symposium effectively highlighted the research of junior and established investigators within the Latin American transplant community and provided a stimulating opening for the Banff Conference.

Findings of Banff Renal Allograft Pathology Working Groups

The findings of BWGs formed in 2009 and 2011, including findings of the Banff initiative for quality assurance in transplantation (BIFQUIT) C4d trial (1), are summarized in Table 1. As findings of four of the six remaining BWGs will soon be submitted for publication, these will not be reviewed further here except for some comments regarding modification of the definitions and thresholds for glomerulitis (g score) and chronic glomerulopathy (cg score) and the introduction of C4d-negative ABMR into the formal Banff classification.

Changes made in glomerulitis and chronic glomerulopathy definitions and thresholds were based on two independent sets of 30 and 17 biopsies (periodic acid-Schiff [PAS] and silver methenamine stains), respectively. These cases, selected to represent the full range of g and cg scores (according to existing Banff criteria [2,3]), were scanned and scored as virtual slides by 21 and 15 pathologists, respectively, who were blinded to clinical and serological data and C4d results. The pathologists had a wide range of experience and specialization. For the first slide circulation, pathologists scored each case according to eight individual sets of definitions and thresholds for the g score and six for the cg score. Only those definitions/thresholds for g (three totals) and cg (two totals) showing the highest kappa scores were used for the second slide circulation.

For glomerulitis, the best inter-observer agreement and correlation with C4d scores, gene expression profiles of

Table 1: Summary of findings of Banff Working Groups

Working group	Isolated v	Glom. lesions	Fibrosis	Implantation biopsy	Polyoma	C4d− ABMR	BIFQUIT
Leader	Banu Sis	Banu Sis	A. Brad Farris	Helen Liapis	Volker Nickeleit	Mark Haas	Michael Mengel
Issues to address	Do these truly represent acute rejection?	Improve inter-observer agreement in scoring of g, cg	Optimize inter-observer agreement in assessment of IF/TA	Inter-observer variability and clinical correlations in wedge vs. core biopsies; frozen vs. paraffin sections	Develop a clinically relevant morphologic classification for polyoma virus nephropathy (PVN)	Consensus criteria for introduction into Banff ABMR classification	Quality assurance trials for C4d and polyoma stains
Group findings	Isolated v shows comparable response to treatment and graft survival as v lesions with i and t. Thus, most isolated v lesions should be reported as type 2 (or 3) acute TCMR. Although C4d+ cases were excluded, 11% and 13%, respectively, of isolated v biopsies were associated with anti-Class I and anti-Class II DSA. Therefore, some isolated v lesions appear to represent acute ABMR or mixed ABMR+TCMR	Revised definition for g (requires endothelial swelling and capillary occlusion). Revised threshold for cg to optimize inter-observer agreement and correlation with C4d, DSA and molecular markers of ABMR, although kappa values for g and cg scoring were fair and moderate, respectively	% Abnormal cortex better than % cortex occupied by fibrous tissue with respect to inter-observer agreement, although kappa value only fair	Frozen section wedge biopsy shows adequate inter-observer agreement, better for glomerular than vascular and tubule-interstitial parameters. Digital images adequate for interpretation	3 Stage scoring for PVN (1, 2, 3) based on % infected (SV40+) tubules and ci score. PVN3 lesions correlated with higher serum creatinine at the time of biopsy and 12 months postbiopsy and were strongly correlated with graft loss	Determined consensus criteria for C4d− ABMR to be incorporated into Banff classification (see Table 2)	Results from the first BIFQUIT C4d trial (Banff Initiative for Quality Assurance in Transplantation) have been published (1) and revealed significant inter-institutional variability for C4d immunohistochemistry
Future plans	Publish findings—examine isolated v lesions in a cohort including C4d+ biopsies	Publish findings—validate new criteria as predictors of graft outcomes	Publish findings—explore possible methods to improve inter-observer agreement	Studies in a larger cohort to examine correlation between biopsy findings and DGF, SCr levels at 6 and 12 months	Publish findings—validation studies in other patient/biopsy cohorts	Correlate new diagnostic categories with clinical outcomes in patients with recurrent versus *de novo* DSA	Follow-up trials with the aim to establish ongoing QA activities for ancillary diagnostic testing in transplantation pathology

ABMR, antibody-mediated rejection; cg, Banff chronic glomerulopathy score; DGF, delayed graft function; DSA, donor-specific antibody; g, Banff glomerulitis score; i, Banff interstitial inflammation score; IF/TA, interstitial fibrosis and tubular atrophy; SCr, serum creatinine; t, Banff tubulitis score; TCMR, T cell–mediated rejection; v, Banff arteritis score.

endothelial activation and injury transcripts (ENDATs) (4), and DSA-selective gene transcript (DSAST) profiles (5) were seen with a definition that includes complete or partial occlusion of ≥1 glomerular capillary by leukocyte infiltration and endothelial cell enlargement (Figure 1). Determination of the numerical g score is still based on the percent of involved glomeruli as previously (2): 1–25%, 26–50% and >50% for g1, g2 and g3, respectively. Scoring of glomerulitis based on these fractions of involved glomeruli using the aforementioned definition was superior to scoring based on numbers of leukocytes per glomerulus, even when CD68 staining was added, although the latter was included only in the second set of biopsies and further investigation may be warranted. Addition of CD68 staining did not improve inter-observer agreement when glomerulitis was scored using the definition that includes endothelial enlargement/capillary occlusion. Whether such agreement would be improved by addition of a threshold number of leukocytes/glomerulus to the current definition, as suggested by Batal et al (6), is an issue for future consideration.

For the cg score, inter-observer agreement was best with scoring based on the fraction of involved glomeruli and a low threshold of glomerular basement membrane (GBM) double contour(s) in ≥1 capillary loops in a single glomerulus, as opposed to the current threshold of ≥10% of capillary loops in the most severely involved glomerulus (2,3). Furthermore, better correlations with anti-class II DSA and ENDATs were seen with the lower threshold.

Inter-observer agreement was fair to moderate for the g score (kappa = 0.31 in the second slide circulation) and somewhat better for the cg score (0.47).

Scoring of cg in these trials was based entirely on light microscopy. However, Wavamunno et al (7) demonstrated that endothelial and GBM lesions detectable within the first 3 months posttransplantation by electron microscopy (EM) are highly correlated with later development of overt transplant glomerulopathy (TG; GBM double contours by light microscopy). Subsequent studies (8–10) and new data presented at the conference by Brian Nankivell have confirmed and extended these findings, demonstrating that endothelial swelling, subendothelial electron-lucent widening and early GBM duplication by EM are highly correlated with DSA. The meeting attendees overwhelmingly favored incorporation of EM findings into the definition of cg as follows:

cg0 – no GBM double contours by light microscopy or EM
cg1a – no GBM double contours by light microscopy but GBM double contours (incomplete or circumferential) in at least three glomerular capillaries by EM with associated endothelial swelling and/or subendothelial electron-lucent widening

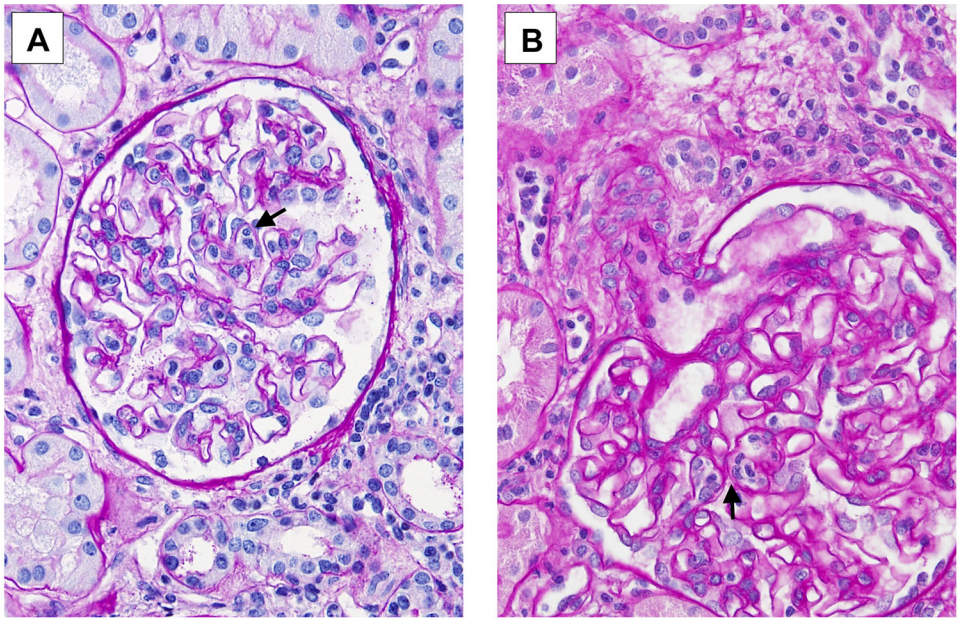

Figure 1: Two examples of glomeruli with segmental glomerulitis, defined as complete or partial occlusion of ≥1 glomerular capillary by leukocyte infiltration and endothelial cell enlargement (arrows). In addition to glomerulitis, the glomerulus in panel B shows transplant glomerulopathy (cg1b) with a small number of glomerular basement membrane double contours in the vicinity of the arrow, and peritubular capillaritis is also present. Periodic acid-Schiff stain, original magnification ×400 (both panels).

cg1b – one or more glomerular capillaries with GBM double contours in ≥1 nonsclerotic glomerulus by light microscopy; EM confirmation is recommended if EM is available.

Lesions meeting criteria for cg1a are included in the revised criteria for chronic, active ABMR (Table 2).

It is recognized that there are transplant centers in different parts of the world without EM facilities, and as such it should be stressed that the use of EM is clearly not mandatory in evaluation of renal allograft biopsies. Still, while many centers with EM capability currently perform EM on renal allograft biopsies only when there is suspicion for a recurrent or *de novo* glomerular disease, its diagnostic value in other clinical circumstances is becoming increasingly apparent. As detailed at the meeting by Ian W. Gibson, the Banff group now recommends that at centers with EM capability, ultrastructural studies should be performed in all biopsies from patients who are sensitized, have documented DSA at any time posttransplantation and/or who have had a prior biopsy showing C4d staining, glomerulitis and/or peritubular capillaritis. It is also advised that EM be considered in all biopsies performed ≥6 months posttransplantation and in for-cause biopsies done ≥3 months posttransplantation to determine if early changes of TG are present, prompting testing for DSA.

Revised Banff Criteria for ABMR in Renal Allografts: Inclusion of C4d-Negative ABMR

Multiple studies in renal allografts reported from different centers, employing standard morphological and molecular approaches, strongly support the existence of ABMR with negative or minimal/equivocal C4d deposition within peritubular capillaries (4,8,11–16). C4d-negative ABMR, defined by microvascular injury (MVI; glomerulitis, peritubular capillaritis, thrombotic microangiopathy) in the presence of DSA, has been reported both in biopsies performed because of graft dysfunction and in protocol biopsies of grafts with stable function (4,8,12–16). The fractions of cases of both acute/active and chronic, active ABMR reported to be ''C4d-negative'' vary considerably between centers, in large part related to their fraction of highly sensitized patients, the method used for C4d staining (immunofluorescence [IF] on frozen sections vs. immunoperoxidase [IP] on paraffin sections of formalin-fixed tissue), and the threshold for C4d positivity. Still, Robert B. Colvin at this meeting reported work from his laboratory (Farkash et al, submitted for publication) showing that even in for-cause biopsies with acute MVI and DSA analyzed by the most sensitive indirect IF method, ~20% of such biopsies show no detectable C4d staining. It was therefore felt overwhelmingly by meeting attendees that C4d-negative ABMR be incorporated into the Banff classification for renal ABMR.

The revised ABMR classification in Table 2 is based on a draft circulated during the meeting to all attendees, and modified during extensive discussions after the meeting. Specific issues considered in formulating and modifying the draft, requiring a consensus within the group, are listed in Table 3. Immunohistopathologic evidence (typically in the form of C4d staining), previously required for diagnosis of ABMR (3), has been replaced by a category of current/recent evidence of antibody interaction with the endothelium, the latter including C4d positivity but also at least moderate MVI or elevated expression in the biopsy tissue of gene transcripts indicative of endothelial injury. The threshold for moderate MVI ($g + ptc \geq 2$) has been documented to be associated with development of overt TG in the presence of DSA, even in C4d-negative cases (8). The consensus of the meeting attendees was that molecular evidence of active endothelial injury in the biopsy tissue should also be included in this category, provided that thorough validation of the molecular test has been performed. This was mainly done to allow the classification to adapt to emerging data, since at present the only molecular marker so validated is ENDAT expression, shown by Sis et al (4) to correlate with development of TG and graft survival even in the absence of C4d. However, even this validation has been limited to a single center, and the use of ENDAT expression at other centers or other test(s) of gene expression within the biopsy as evidence of ABMR must first undergo independent validation as was done by Sis et al (4) for ENDATs. Finally, the histologic criteria for acute ABMR now include intimal arteritis. This is based on studies of Lefaucheur et al (21) that were recently published and presented at the meeting. In ABMR, intimal arteritis is associated with an inferior prognosis; however, these lesions are more commonly associated with mixed ABMR/TCMR (72% and 63% had interstitial inflammation and tubulitis, respectively [21]) than with ''pure'' ABMR, and may also be seen in pure TCMR in the absence of DSAs. In addition, intimal arteritis in the presence of DSA is only infrequently seen (8 of 64 cases in Lefaucheur et al [21]) in the absence of glomerulitis and/or peritubular capillaritis.

Finally, documentation of DSA should be done using methods validated for optimal sensitivity, specificity and reproducibility within and across laboratories. For antibodies to HLA classes I and II, this should ideally be a solid-phase assay. This applies not only to ABMR in renal allografts but also recipients of all solid organ transplants being evaluated for possible ABMR.

New Banff Renal Working Groups

These working groups, described in Table 4, arose directly from presentations and discussions at the conference.

Findings of Mengel et al and from the DeKAF study (23,24), the latter presented at the meeting by Roz Mannon, have shown that interstitial inflammation in areas of interstitial

Table 2: Revised (Banff 2013) classification of antibody-mediated rejection (ABMR) in renal allografts

Acute/active ABMR; all three features must be present for diagnosis[1,2]

1. Histologic evidence of acute tissue injury, including one or more of the following:
   Microvascular inflammation ($g > 0$[3] and/or $ptc > 0$)
   Intimal or transmural arteritis ($v > 0$)[4]
   Acute thrombotic microangiopathy, in the absence of any other cause
   Acute tubular injury, in the absence of any other apparent cause
2. Evidence of current/recent antibody interaction with vascular endothelium, including at least one of the following:
   Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by IF on frozen sections, or $C4d > 0$ by IHC on paraffin sections)
   At least moderate microvascular inflammation ($[g + ptc] \geq 2$)[5]
   Increased expression of gene transcripts in the biopsy tissue indicative of endothelial injury, if thoroughly validated[6]
3. Serologic evidence of donor-specific antibodies (DSAs) (HLA or other antigens)

Chronic, active ABMR; all three features must be present for diagnosis[1,7]

1. Morphologic evidence of chronic tissue injury, including one or more of the following:
   Transplant glomerulopathy (TG) ($cg > 0$)[8], if no evidence of chronic thrombotic microangiopathy
   Severe peritubular capillary basement membrane multilayering (requires EM)[9]
   Arterial intimal fibrosis of new onset, excluding other causes[10]
2. Evidence of current/recent antibody interaction with vascular endothelium, including at least one 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 ($[g + ptc] \geq 2$)[5]
   Increased expression of gene transcripts in the biopsy tissue indicative of endothelial injury, if thoroughly validated[6]
3. Serologic evidence of DSAs (HLA or other antigens)

C4d staining without evidence of rejection; all three features must be present for diagnosis[11]

1. Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by IF on frozen sections, or $C4d > 0$ by IHC on paraffin sections)
2. $g = 0$, $ptc = 0$, $cg = 0$ (by light microscopy and by EM if available), $v = 0$; no TMA, no peritubular capillary basement membrane multilayering, no acute tubular injury (in the absence of another apparent cause for this)
3. No acute cell-mediated rejection (Banff 97 type 1A or greater) or borderline changes

cg, Banff chronic glomerulopathy score; EM, electron microscopy; ENDAT, endothelial activation and injury transcript; g, Banff glomerulitis score; GBM, glomerular basement membrane; IF, immunofluorescence; IHC, immunohistochemistry; ptc, peritubular capillary; TCMR, T cell–mediated rejection; v, Banff arteritis score.

[1]For all ABMR diagnoses, it should be specified in the report whether the lesion is C4d-positive (C4d2 or C4d3 by IF on frozen sections; $C4d > 0$ by IHC on paraffin sections) or without evident C4d deposition (C4d0 or C4d1 by IF on frozen sections; C4d0 by IHC on paraffin sections).

[2]These lesions may be clinically acute, smoldering or subclinical. Biopsies showing two of the three features, except those with DSA and C4d without histologic abnormalities potentially related to ABMR or TCMR (C4d staining without evidence of rejection; see footnote 11, below) may be designated as ''suspicious'' for acute/active ABMR.

[3]Recurrent/*de novo* glomerulonephritis should be excluded.

[4]It should be noted that these arterial lesions may be indicative of ABMR, TCMR or mixed ABMR/TCMR. ''v'' lesions are only scored in arteries having a continuous media with two or more smooth muscle layers.

[5]In the presence of acute TCMR, borderline infiltrates or evidence of infection, ptc $\geq$2 alone is not sufficient to define moderate microvascular inflammation and g must be $\geq$1.

[6]At present the only validated molecular marker meeting this criterion is ENDAT expression (4), and this has only been validated in a single center (University of Alberta). The use of ENDAT expression at other centers or other test(s) of gene expression within the biopsy as evidence of ABMR must first undergo independent validation as was done for ENDAT expression by Sis et al (4).

[7]Lesions of chronic, active ABMR can range from primarily active lesions with early TG evident only by EM (cg1a) to those with advanced TG and other chronic changes in addition to active microvascular inflammation. In the absence of evidence of current/recent antibody interaction with the endothelium (those features in the Second Section), the term active should be omitted; in such cases DSA may be present at the time of biopsy or at any previous time posttransplantation.

[8]Includes GBM duplication by EM only (cg1a) or GBM double contours by light microscopy.

[9]$\geq$7 layers in one cortical peritubular capillary and $\geq$5 in two additional capillaries (17), avoiding portions cut tangentially.

[10]While leukocytes within the fibrotic intima favor chronic rejection, these are seen with chronic TCMR as well as chronic ABMR, and are therefore helpful only if there is no history of TCMR. An elastic stain may be helpful as absence of elastic lamellae is more typical of chronic rejection and multiple elastic lamellae are most typical of arteriosclerosis, although these findings are not definitive.

[11]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 (18,19) and may represent accommodation. However, with anti-HLA antibodies such lesions may progress to chronic ABMR (20) and more outcome data are needed.

Table 3: Consensuses reached in development of the revised Banff classification of antibody-mediated rejection (ABMR)

1. ABMR (both acute/active and chronic, active) may now be diagnosed in the absence of C4d deposition. However, in the absence of C4d, additional evidence of current or recent antibody interaction with the vascular endothelium must be present; this will help avoid overdiagnosis of ABMR. Such evidence may be morphologic, in the form of at least moderate microvascular inflammation, or molecular, as detailed in Table 2 and in the text.

2. As the criteria in Table 2 apply to both for-cause and protocol biopsies, and because similar biopsy findings may be seen in acute and smoldering lesions of ABMR, the term ''acute/active'' is used rather than just ''acute.'' Further studies are needed to directly compare graft outcomes in patients diagnosed with acute/active ABMR in different clinical settings, as well as with preformed/recurrent versus *de novo* DSAs. Where deemed appropriate the pathologist may comment that the biopsy findings and clinical circumstances suggest a lesion that is acute or smoldering. Likewise, a comment may be made as to the relative activity and chronicity in cases of chronic, active ABMR.

3. Intimal arteritis (v1 and v2) should be included among lesions satisfying histologic criteria for ABMR, based on findings of Lefaucheur et al (21) that were recently published and presented at the 2013 Banff meeting. In ABMR, intimal arteritis is associated with an inferior prognosis; however, these lesions are more commonly associated with mixed ABMR/TCMR than with ''pure'' ABMR, and may also be seen in pure TCMR in the absence of DSAs. Intimal arteritis may be the only histologic manifestation of ABMR, although this quite uncommon (8 of 64 cases with DSA and intimal arteritis in Lefaucheur et al [21] lacked glomerulitis and peritubular capillaritis).

4. Diffuse (C4d3) and focal (C4d2) peritubular capillary C4d staining by IF and IP as well minimal (C4d1) staining by IP should be considered C4d-positive, the latter because of the lower sensitivity of staining by IP on paraffin sections (22) and evidence that C4d1 by IP is associated with microvascular inflammation (11). There was disagreement on whether to consider C4d1 on frozen sections as C4d-positive; a small majority felt it should not be although the clinical significance of C4d1 needs further investigation.

DSA, donor-specific antibody; IF, immunofluorescence; IP, immunoperoxidase; TCMR, T cell–mediated rejection.

Table 4: New Banff Renal Working Groups and proposed questions to be addressed

T Cell–Mediated Rejection (TCMR) Working Group

1. Should the ti score be included in the classification for TCMR diagnosis? Options include:
   As a replacement for the i score
   As part of a new category of chronic/active TCMR
   Recommend inclusion of ti score in the diagnosis line, possibly with a comment as to its prognostic significance, but do not change the current TCMR classification
2. Should the borderline category be modified to try and identify those lesions most specific for active TCMR? Options include:
   By assessing edema and tubular injury (as in CCTT classification)
   By including immunohistochemical stains (e.g. granzyme B)
   By assessing the extent of tubulitis (as in CCTT classification)
   By inclusion of molecular data where available, and if so what are the most useful transcripts/transcript sets to examine?
3. Are there clinical and pathological differences in borderline infiltrates in for-cause versus protocol biopsies?

Clinical and Laboratory Assessment of Highly Sensitized Patients Working Group

1. Develop evidence-based recommendations for transplantation of patients with broad sensitization and high titer DSAs, for whom the only transplant option is desensitization
   How frequently to monitor DSA?
   Role of protocol biopsies, when (and to how far out posttransplant) should these be done?
   Should an increase in DSA without a change in graft function prompt a biopsy, and if so should a specific minimum mean fluorescence intensity (MFI) be required?
   What are the minimal capabilities a center needs to have to support care for these patients (including but not limited to HLA lab/pathology evaluation and turn-around time, available therapies, specialized personnel)?
2. Systematically evaluate possible differences in ABMR (clinically, serologically, pathologically and from a molecular standpoint) in this group of patients versus those of other sensitized patients and of nonsensitized patients with *de novo* DSA that may be relevant to how the patients are treated

Working Group for Evaluation of Adjunctive Diagnostics in Renal Allograft Biopsy Interpretation

1. Develop consensus guidelines for circumstances under which it is advisable to perform serologic testing for DSAs and molecular analysis on renal biopsy tissue, serum and/or urine collected at the time of biopsy
2. Generate consensus for applicable molecular markers and marker panels that are associated with improved diagnostic precision and/or prediction of clinical outcomes
3. Develop and conduct multicenter molecular studies for specific diagnostic circumstances (e.g. early and late ABMR without evident C4d deposition, borderline lesions, assessment of donor biopsies), including assessment of inter-center assay reproducibility

ABMR, antibody-mediated rejection; i, Banff interstitial inflammation score; ti, Banff total interstitial inflammation score.

fibrosis and tubular atrophy (IF/TA), although not contributory toward a diagnosis of acute TCMR by current Banff criteria (3), is deleterious to the graft, more so than IF/TA not associated with inflammation. Furthermore, the score of total inflammation in sclerotic and nonsclerotic areas of the cortex (ti score) was found to be more predictive of graft loss than the Banff i score (inflammation in nonscarred areas) (23). The general consensus at the meeting was that total cortical inflammation, including that in areas of IF/TA, should, when present, be included in the diagnosis line of the renal allograft biopsy report. However, it is premature to decide if the ti score should be considered as contributing to a diagnosis of acute (or chronic, active) TCMR. A TCMR working group was formed to address this question as well as the continuing dilemma of assessing the clinical significance of borderline inflammatory infiltrates.

The second new working group represents the first BWG with primarily clinical objectives, stemming from discussions regarding the clinical approach to broadly sensitized patients whose only real option for transplantation is desensitization. This group will consist of clinicians, clinical immunologists and pathologists, the latter to evaluate possible differences in ABMR in this group of patients versus those of nonsensitized patients with *de novo* DSA that may be relevant to treatment.

Finally, a new working group was formed to identify and validate clinically relevant and diagnostically useful molecular markers for use in renal allograft biopsy evaluation, and develop consensus guidelines for circumstances in which it is most advisable to employ these markers as well as DSA testing.

Developments in Other Solid Organ Allografts

Heart allografts

Stains used for diagnosis of ABMR in heart allografts include anti-C4d and anti-C3d. Biopsies positive for C4d (C4d+) and C3d (C3d+) are strongly associated with DSA and allograft dysfunction, while cases with episodes that are only C4d-positive are mostly subclinical (i.e. no allograft dysfunction) (25,26). On a morphologic basis, it is not possible to designate the latter as accommodation versus subclinical ABMR. In a prospective study of a large cohort, ~17% of patients who are C4d+ progressed to C4d+ and C3d+. There is still a gap in knowledge about the consequences of C4d+ only cases for adult and pediatric cardiologists. There is also uncertainty about the management of subclinical ABMR and how to differentiate subclinical from clinical ABMR. To this end, the American Heart Association will be publishing a scientific statement evaluating clinical and pathological evidence regarding ABMR.

The 2013 International Society for Heart & Lung Transplantation (ISHLT) Working Formulation for ABMR (27) has been accepted for publication. In this evolving formulation, ABMR is proposed to be diagnosed by evaluating histopathologic changes on H&E-stained sections if present (pathologic ABMR based solely on histologic changes, termed pAMR1 [H+]). The usefulness of the histologic diagnosis of ABMR, including microvascular inflammation, was discussed with illustrative cases in the heart session. Presently, the clinical significance of pAMR1 (H+), characterized by histologic but not immunohistologic evidence of ABMR, is not known although the group agreed there should not be many cases of pAMR1 (H+). There are currently no studies to suggest that pAMR1 (H+) represents C4d-negative ABMR. The category pAMR1 (I+) refers to cases with immunopathologic (by IF or immunohistochemistry) evidence of ABMR but no such evidence by routine histology. It is a compromise between those who use immunohistochemistry and IF. Immunohistochemistry users do not report C3d. Thus, the differentiation between C4d+ and C3d+ and C4d+ only is lost within this category. A major problem with this working formulation involves language that specifically prevents pathologists from considering the presence or absence of DSA and/or allograft dysfunction in the diagnostic criteria of ABMR.

Last, while studies of cardiac ABMR have assumed a direct causality between ABMR and cardiac allograft vasculopathy (CAV), there is no hard evidence of this. Furthermore, there is no systematic study of antibody-dependent cellular cytotoxicity (ADCC) as an alternative mechanism linking antibodies to CAV.

Liver allografts

The liver sessions focused on areas related to acute and possible chronic manifestations of ABMR. Current literature and a Banff survey show that most large centers recognize acute ABMR, which manifests primarily as MVI and inflammation combined with diffuse portal microvascular (formalin-fixed, paraffin-embedded tissue) or sinusoidal (frozen tissue) C4d deposition and exclusion of other insults causing a similar pattern of injury. Currently, recognized acute ABMR occurs in small percentage (<10%) of sensitized recipients, usually those with very high titer DSA often of the IgG3 subclass. Clinical/serological clues of ABMR include persistent serum DSA (anti-class I DSA usually resolve), refractory thrombocytopenia, circulating immune complexes and otherwise unexplained hyperbilirubinemia. Chronic liver allograft ABMR has not yet been as rigorously defined as acute ABMR, but emerging literature suggests DSA can be associated with more rapidly progressive fibrosis in hepatitis C–positive recipients with recurrent hepatitis, diminished long-term graft and patient survival and indolently progressive perivenular and perivenular subsinusoidal fibrosis. However, other insults causing similar patterns of fibrosis must be excluded. Initial studies suggest that adverse consequences of DSA in liver transplantation are directly related to complement-fixing and Fc receptor-binding/activation characteristics (IgG3 >

Table 5: Conclusions of ISHLT Pathology Council survey of current practices on the use of C4d antibody stains in the diagnosis and reporting of pulmonary ABMR

1. The diagnosis of pulmonary ABMR requires a multi-disciplinary approach
2. The histopathological findings in ABMR are generally nonspecific patterns of acute injury
3. Staining for C4d should be triggered by these patterns of acute injury
4. Qualified terminology should be used in reporting the relevance of the C4d staining to the final diagnosis
5. Protocols for studies of donor-specific antibody timed to biopsies should be performed by all lung transplant centers
6. Investigations addressing issues of time to onset of ABMR, incidence, prevalence, spectrum of temporal, morphological and immunopathological changes, clinical outcomes and risk for chronic allograft dysfunction are encouraged

ABMR, antibody-mediated rejection; ISHLT, International Society for Heart & Lung Transplantation.
Adopted from Berry et al (32).

IgG1 > IgG2 > IgG4). High titer IgG3 recipients more often show adverse consequences, whereas exclusively non-IgG3/IgG1 DSA appears in some, but not all, stable, operationally tolerant recipients weaned from immunosuppression. A document is being prepared which will include recommendations for tissue sampling and monitoring, consensus criteria for ABMR and areas requiring further development.

Pancreas allografts

Four main topics were presented at the pancreas session.

Difficulties regarding diagnosis of ABMR, with emphasis on the heterogeneity of clinical and pathological presentations: Data were presented from a study soon to be published, describing the incidence, risk factors and outcomes of ABMR (28). Subsequently, a series of cases were presented illustrating the potential variability with respect to C4d positivity, DSA studies and morphological spectrum including the morphological evolution and impact of treatment. Preliminary studies were presented describing the potential association of rejection-related vascular lesions with ABMR.

Utilization of biopsies of the grafted duodenal cuff as surrogates for diagnosis of acute pancreas allograft rejection (29): Initial results were presented on prospective analysis of endoscopic biopsies of the duodenal patch, and on retrospective studies of archival tissue.

Studies on immunophenotyping of inflammatory infiltrates in pancreas allograft biopsies: Studies presented at this session demonstrated that immunostains can enhance the understanding of TCMR and ABMR. However, accurate diagnosis of the grade and type of rejection rests mainly on the systematic evaluation of morphological features on routinely stained sections according to published guidelines (30).

Recognition of islet pathology in whole pancreas allografts: Islet diseases leading to intermediate to late graft failure independently of allograft rejection were discussed and strategies to raise awareness of these processes were proposed.

Lung allografts

This session focused on reviewing literature related to the pathology of ABMR and preliminary data from the Banff study on lung biopsy findings in patients with DSA (31). The ISHLT Pathology Council survey on C4d stains in the diagnosis of pulmonary ABMR (32) was reviewed (Table 5). Discussion of the association of preformed and *de novo* DSA with various forms of antibody-mediated injury to the lung allograft suggested that early detection of DSA following lung transplantation and systematic monitoring with sensitive solid-phase platforms are recommended (33). The clinical overview of pulmonary ABMR was presented and overall conclusions revealed that to date survival is poor after ABMR, but improved with rapid clearance of the antibodies (34).

Finally, preliminary results from an international Banff study group of 10 pulmonary pathologists on the pathology of lung ABMR were presented and discussed. The study consisted of 265 lung transplant biopsies performed within 30 days of *de novo* DSA detection. Slides were digitally scanned and reviewed by all study participants. Early data suggest that both acute lung injury and capillary neutrophilic inflammation correlate with *de novo* DSA in these patients. Results also suggested that diffuse C4d staining in these biopsies was specific for *de novo* DSA, but was rare (7 in 265 biopsies) and therefore an insensitive marker for ABMR in the lung.

Vascularized composite allografts

This session focused on reviewing acute and chronic changes and clinicopathological features of skin in vascularized composite allograft (VCA) other than rejection. Studies in preclinical models showed chronic changes including skin and muscle atrophy, sclerotic bone (35), and vessel wall fibrosis (36). Clinical cases presented at this session demonstrated intimal proliferation, loss of hair follicles, nail changes (37) and skin sclerosis. Comparisons between vascular changes after a VCA and after autologous replantation were discussed. Specifically, histologic changes of arteries 3 years after hand replantation have shown fibromuscular proliferation and intimal neovascularization with marked intimal thickening (38). The roles of ischemia-reperfusion injury and secondary surgeries in both settings as well as the presence of rejection immediately following trauma were discussed. Current observations are

that chronic VCA rejection is more similar than different from that in other organ transplants. Areas of investigation discussed include the specificities in VCA compared with other transplants, the role of the microvasculature, the role of complement, the differential diagnosis of inflammation and biomarkers. It was agreed to review and collect data for potential changes to the VCA-Banff system at future meetings.

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Disclosure

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Appendix

Banff 2013 meeting faculty

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Speakers at the Latin American Symposium on Transplant Immunobiology and Immunopathology (the Transplantation Society KOL–NKOL meeting)

Invited guests: Colvin, Robert B. (USA), Glotz, Denis (France), Opelz, Gerhard (Germany), Zeevi, Adriana (USA).

Key opinion leaders (KOLs): Azeka, Estela (Brazil), Benvenuti, Luiz Alberto (Brazil), Bicalho, Maria Das Gracas (Brazil), Buenrostro, Luis E. Morales (Mexico), Camara, Niels Olsen Saraiva (Brazil), Castro, Maria Cristina R. (Brazil), David, Daisa S. R. (Brazil), David-Neto, Elias (Brazil), Delucchi, Angela (Chile), Garcia-Gallont, Rudolf (Guatemala), Goldberg, Julio (Argentina), Keitel, Elizete (Brazil), Lima, Maria Gerbase (Brazil), Malheiros, Denise Maria (Brazil), Neumann, Jorge (Brazil), Orozco, Carlos (Columbia), Raffaele, Pablo M. (Argentina), Susin, Michele F. (Brazil), Tanus, Roberto (Argentina), Uribe, Norma Ofelia (Mexico).

New key opinion leaders (NKOLs): Alonso, Nestor F. Pedraza (Columbia), Barbosa, Erick Acerb (Brazil), Bringhenti, Rafael (Brazil), Bruno, Rosana Mussoi (Brazil), Farhat, Juliana (Brazil), Glehn-Ponsirenas, Renata (Brazil), Grenzi, Patricia Cristina (Brazil), Hauer, Venessa (Brazil), Messias, Mariana (Argentina), Pegas, Karla Lais (Brazil), Pereira, Andre (Brazil), Petroni, Jorgelina (Argentina), Rodgigues, Georgina L. (Brazil), Rojo, Angelica (Chile), Silva, Marina Burgos (Brazil), Souza, Patricia Soares (Brazil), Tanigawa, Ryan Yukimatsu (Brazil), Vazquez, Lluvia A. Marino (Mexico).