BANFF HIGHLY SENSITIZED WORKING GROUP UPDATE

Banff Conference on Allograft Pathology

March 2017

Barcelona, Spain

Edward Kraus MD on behalf of the Highly Sensitized Working Group

Johns Hopkins Baltimore, USA

Highly Sensitized Working Group - Goals (2013)

Issues to address:

- Define criteria for highly sensitized patients
- Determine consensus for what personnel and facilities are needed for centers to perform transplantation in highly sensitized recipients
- Standardize the definitions related to management of sensitized transplant recipients

Previous work (presented at Banff 2015)

1st project: Survey of current practices

Three separate surveys

- Pathologists
- Transplant clinicians (nephrologists/surgeons)
- HLA laboratory directors (survey reviewed and approved by ASHI)

- Questions about DSA testing and cut-offs, biopsy practices and reporting, desensitization and immunosuppression
- Only one response accepted per transplant center or pathology group

Highly Sensitized Working Group Take Home Messages (2015)

- We needed a clear definition of sensitized and highly sensitized patients
- Immune modulation/desensitization practices were varied
- The timing of kidney allograft protocol biopsies were not uniform

Highly Sensitized Working Group Take Home Messages (2015)

- Testing and reporting of HLA antibody and DSA levels varied
- Less than half of HLA laboratories tested for prozone/interference in solid phase antibody assays
- Consistent practice patterns and definitions regarding DSA and sensitization were needed to improve:
  - The diagnosis of ABMR
  - The identification of patients at high risk for allograft loss
  - Clinical trial development

2nd project (2016-2017):
How does the Banff reporting system translate into clinical practice?

Objectives

- Understand how clinicians interpret current Banff nomenclature for the diagnosis of antibody mediated rejection.
- Learn how clinicians are currently treating patients with antibody mediated rejection in a variety of settings.
- Determine whether clinicians and pathologists interpret Banff nomenclature differently.

- Workgroup Co-chair
  - Carrie Schinstock MD
  - Mayo Clinic, Rochester, MN

Special Thanks

Ruth Sapir-Pichhadze, BMedSc, MD, MSc, PhD, FRCPC
McGill University
Toronto, Canada

Helped distribute surveys to Canadian Transplant Centers

Working group members

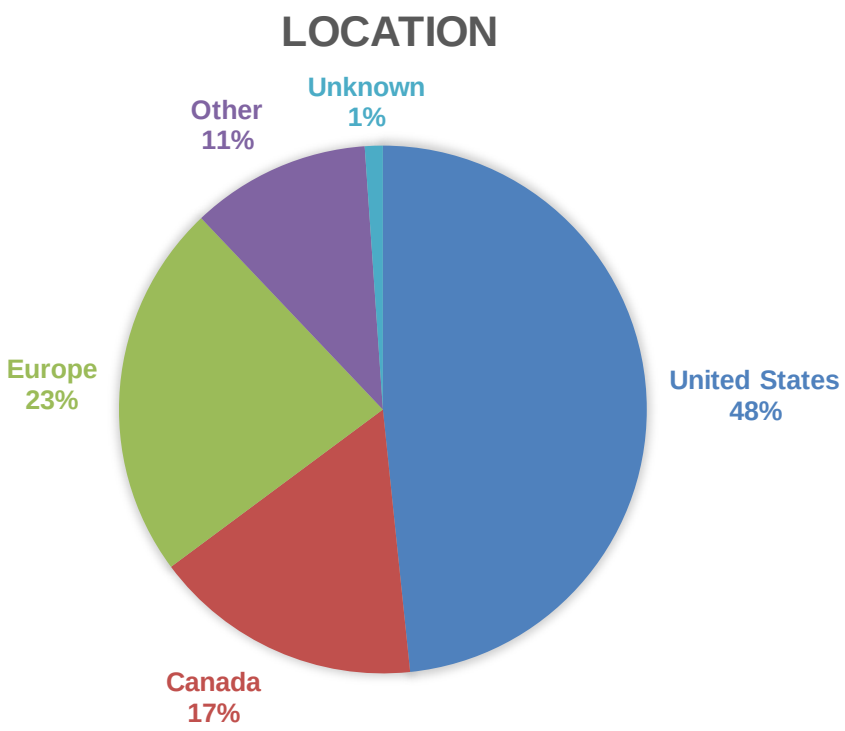
Khalid Almeshari	King Faisal Hosp, Riyadh, Saudi Arabia
Medhat Askar	Cleveland Clinic, Cleveland, USA
Serena Bagnasco*	Johns Hopkins, Baltimore, USA
Manju Balasubramanian	Einstein, New York, USA
Ibrahim Batal	Columbia U, New York, USA
Laurine Bow	Yale U, New Haven, USA
Patricia Campbell	U Alberta, Edmonton, Canada
Matthew Cooper	Georgetown, Washington DC, USA
Lynn Cornell*	Mayo Clinic, Rochester, MN, USA
Emanuele Cozzi	Universita di Padova, Italy
Darshana Dadhania*	Cornell U, New York, USA
Amira Gohara	University of Toledo, USA
Daga Sunil	University Hospital, Coventry, UK
Mark Haas	Cedars Sinai, Los Angeles, USA
Annette Jackson	Johns Hopkins, Baltimore, USA
Basit Javaid	Georgetown, Washington DC, USA
Edward Kraus*	Johns Hopkins, Baltimore, USA
Alexander Loupy	Necker Hospital, Paris, France
Gilbert Moeckel	Yale U, New Haven, USA
Nasreen Mohamed	King Fahad Specialist Hospital, Dammam, Saudi Arabia
Maarten Naesens	Leuven, Belgium
Cuong Nguyen	U of Tennessee, Memphis, USA
Marion Rabant	Necker Hospital, Paris, France
Ruth Sapir-Pichhadze	Montreal, Canada
Carrie Schinstock*	Mayo Clinic, Rochester, MN, USA
Anke Schwarz	Hannover, Germany
Barry Stokes	Columbia U, New York, USA

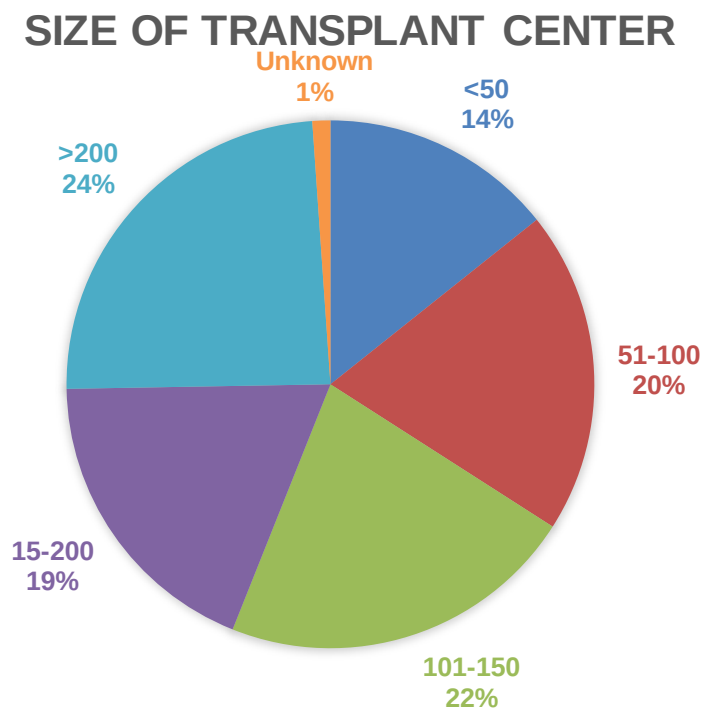
*Co-chairs

Survey

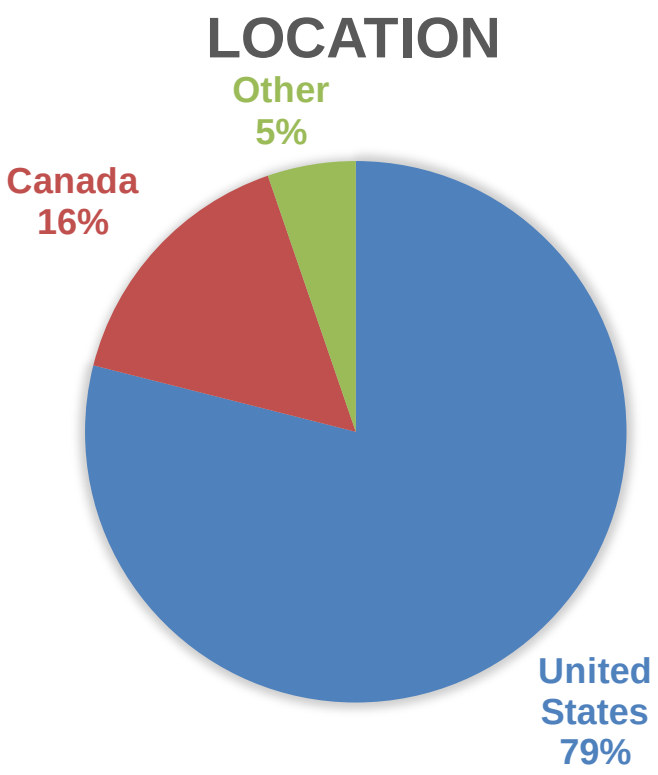
- 6 common clinical scenarios
  - Diagnosis
  - Treatment Plan
- Participants
  - 541 clinicians (91 responses)
  - 88 pathologists (20 responses)
- National & international groups surveyed
  - AST Kidney Pancreas Community of Practice
  - Canadian Society of Transplantation
  - Canadian Society of Nephrology
  - Canadian Network of Transplant Research Program
  - Banff members

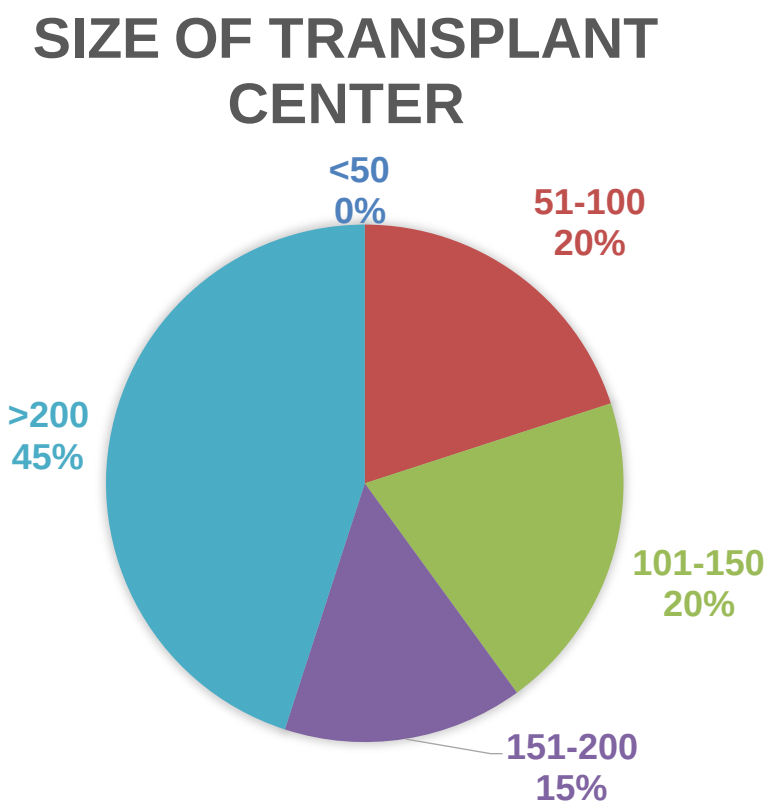
91 Clinician Responses





20 Banff Pathologist Responses





Scenario 1:

- 54 year old male
- Time post-transplant: **4 years**
- Baseline immune risk: **negative cross-match and no DSA**
- Current presentation**: allograft dysfunction and de novo DSA**

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- **Biopsy** - No interstitial inflammation, fibrosis, or tubular atrophy
  - **g score = 2**
  - **ptc score = 1**
  - **cg score = 1**
  - **positive C4d**

Active AMR with associated mild chronic changes

Scenario 1: Diagnosis

	Clinician Diagnosis N=91	Pathologist Diagnosis N=20	P-value
Acute, Active AMR	(43) 47.2%	(3) 15%	P=0.01
Chronic, active AMR	(47) 51.6%	(16) 80%	P=0.03
Other	(1) 1.0%	(1) 5%	P=0.33

Scenario 1: Diagnosis

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- **Clinician and Pathology Responses are different**
- **Clinicians less often recognized chronic AMR (Banff cg score > 0 or C4d+)**

Clinician Treatment based on Diagnosis

	Acute AMR N=42	Chronic AMR N=47	P-value
Plasmapheresis, IVIG, Steroids +/- bortezomib	38 (90.5%)	24 (51.1%)	P<0.01
Steroids +/- IVIG	3 (7.1%)	13 (27.7%)	P=0.01
Conservative Management	0 (0%)	8 (17.0%)	P<0.01
Other	1 (2.4%)	2 (4.3%)	P=1.0

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Other	1 (2.4%)	2 (4.3%)	P=1.0

- **The treatment regimens differ by the clinician's diagnosis**
- **Varied treatment regimens if diagnosis was chronic AMR**
- **Clinicians favored very aggressive treatment despite lack of published efficacy**

Scenario 2:

- 22 year old female
- Time post-transplant: **3 years**
- Baseline immune risk: **negative cross-match and no DSA**
- Current presentation**: allograft dysfunction and de novo DSA**

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- Time post-transplant: **3 years**
- Baseline immune risk: **negative cross-match and no DSA**
- Current presentation**: allograft dysfunction and de novo DSA**
- **Biopsy** - No interstitial inflammation, fibrosis, or tubular atrophy
  - **g score = 1**
  - **ptc score = 2**
  - **cg score = 0**
  - **negative C4d**

Active AMR and negative C4d with no chronic changes on biopsy

Scenario 2 Diagnosis

	Clinician Diagnosis N=91	Pathologist Diagnosis N=20	P-value
Acute, Active AMR	(59) 64.8%	(17) 85.0%	P=0.11
Chronic, active AMR	(26) 28.6%	(1) 5.0%	P=0.04
No AMR	(5) 5.5%	(0) 0.0%	P=0.58
Other	(1) 1.1%	(2) 10.0%	P=0.08

Scenario 2 Diagnosis

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Chronic, active AMR	**(26) 28.6%**	**(1) 5.0%**	P=0.04
No AMR	(5) 5.5%	(0) 0.0%	P=0.58
Other	(1) 1.1%	(2) 10.0%	P=0.08

- **Clinicians and Pathologists differ on chronic, active AMR diagnosis**
- **Clinicians more likely to consider "chronic, active AMR" in setting of C4d negative cases**

Scenario 3: Diagnosis

- 45 year old male
- Time post-transplant: **10 years (deceased donor transplant)**
- Baseline immune risk: **unknown baseline DSA**
- Current presentation**: allograft dysfunction, proteinuria and DSA discovered**

Scenario 3: Diagnosis

- 45 year old male
- Time post-transplant: **10 years (deceased donor transplant)**
- Baseline immune risk: **unknown baseline DSA**
- Current presentation**: allograft dysfunction, proteinuria and DSA discovered**
- **Biopsy** - No interstitial inflammation, tubulitis, fibrosis, or tubular atrophy
  - **ptc score =2**
  - **g score = 1**
  - **cg score = 1**
  - **C4d is negative**

Active antibody mediated injury and negative C4d with mild chronic changes on biopsy 10 years post transplant

Scenario 3:

	Clinician Diagnosis N=91	Pathologist Diagnosis N=20	P-value
Acute, Active AMR	**(15) 16.5%**	**(2) 10.0%**	P=0.73
Chronic, active AMR	**(70) 76.9%**	**(17) 85.0%**	P=0.55
Other	(2) 2.2%	(1) 5.0%	P=0.45

Clinicians much more likely to diagnose this *chronic*, active AMR likely because of the 10 year interval post-transplant

Scenario 4

- 62 year old female with a history of 2 failed kidney transplants
- Time post-transplant: **1 year**
- Baseline immune risk: **Negative crossmatch**
- Current presentation**: Stable allograft function and no DSA**
- **Biopsy**
  - ptc score = 2
  - g score = 2
  - negative C4d
  - No interstitial inflammation, tubulitis, interstitial fibrosis, or tubular atrophy

Microvascular inflammation in highly sensitized patient without detected DSA

Scenario 4 Diagnosis:

	Clinician Diagnosis N=91	Pathologist Diagnosis N=20	P-value
Acute, Active AMR	(12) 13.2%	(1) 5.0%	P=0.45
Chronic AMR	(7) 7.7%	(1) 5.0%	P=1.0
Depends on whether anti HLA testing positive	(42) 46.2%	(12) 60.0%	P=0.32
No AMR	(19) 20.1%	(1) 5.0%	P=0.11
Other	(7) 7.7%	(5) 25.0%	
Unanswered	(4) 4.4%	(0) 0%	

Scenario 4 Diagnosis:

	Clinician Diagnosis N=91	Pathologist Diagnosis N=20	P-value
Acute, Active AMR	(12) 13.2%	(1) 5.0%	P=0.45
Chronic AMR	(7) 7.7%	(1) 5.0%	P=1.0
Depends on whether anti HLA testing positive	**(42) 46.2%**	**(12) 60.0%**	P=0.32
No AMR	**(19) 20.1%**	**(1) 5.0%**	P=0.11

- **20% of clinicians did not think that this was AMR despite microvascular inflammation in sensitized patient**
- **Diagnosis depends on non-HLA testing which has multiple limitations**

Scenario 5

- 56 year old male
- Time post-transplant: **6 months**
- Baseline immune risk: **Positive crossmatch**
- Current presentation**: Stable allograft function and positive DSA**

Scenario 5

- 56 year old male
- Time post-transplant: **6 months**
- Baseline immune risk: **Positive crossmatch**
- Current presentation**: Stable allograft function and positive DSA**
- **Biopsy** - No interstitial inflammation, tubulitis, or tubular atrophy
  - **ptc score =2**
  - **g score =2**
  - **negative C4d**

- **Active antibody mediated injury in setting of positive cross-match kidney transplantation**

Scenario 5 Diagnosis:

	Clinician Diagnosis N=91	Pathologist Diagnosis N=20	P-value
Acute, Active AMR	**(51) 56.0%**	**(15) 75.0%**	P=0.14
Chronic AMR	**(27) 29.7%**	**(2) 10.0%**	P=0.09
Other	(13) 14.3%	(5) 25.0%	P=32

Scenario 5 Diagnosis:

	Clinician Diagnosis N=91	Pathologist Diagnosis N=20	P-value
Acute, Active AMR	(51) 56.0%	(15) 75.0%	P=0.14
Chronic AMR	**(27) 29.7%**	(2) 10.0%	P=0.09
Other	(13) 14.3%	(5) 25.0%	P=32

- **? Due to lack of C4d**
- **? Positive cross-match at time of transplantation**

Scenario 6

- 35 year old male
- Time post-transplant: **18 months**
- Baseline immune risk: **Negative crossmatch**
- Current presentation**: Allograft dysfunction and new DSA**
- **Biopsy**
  - Ptc score =2
  - G score = 1
  - Cg score = 0
  - C4d is negative
  - Banff grade 1 B acute cellular

- **Mixed acute cellular rejection and antibody mediated injury**
- **De novo DSA**

Scenario 6 Diagnosis:

	Clinician Diagnosis N=91	Pathologist Diagnosis N=20
Acute Cellular Rejection Only	(9) 9.9%	(0) 0%
Mixed ACR/AMR	(81) 89.0%	(19) 95.0%
Unanswered	(1) 1.1%	(0) 0%
Other	(0) 0%	(1) 5.0%

Clinicians and Pathologists have similar diagnosis in setting of a mixed rejection

Conclusion

- Clinicians have varied interpretations of the current Banff nomenclature for antibody mediated rejection
- Clinicians and Pathologists interpret the Banff nomenclature differently
- Efforts are needed by the Banff community to improve the consistency in the nomenclature
  - The term “acute” is confusing
  - Current nomenclature does not take into account the timing of injury or development of DSA

Next Steps by the Banff Highly Sensitized Working Group

- Publish Findings
- Consider nomenclature changes to “antibody mediated injury”
  - Rather than “active acute”
    - Consider adding a timing component - i.e. Early acute AMR
    - Define “acute” based on clinical setting (identification of triggering events for development of DSA or documentation of temporal changes of pathology/antibody metrics) – “Suspicious of”
  - Introduce concept of possible AMR diagnosis in setting of microvascular inflammation even without detected DSA in a sensitized or nonsensitized patient
- Knowledge dissemination:
  - Webinar
  - Consensus document