XVIth Banff Meeting Allograft pathology, Banff Canada 19th-23rd September 2022
Joint meeting with the Canadian Society of Transplantation

Kidney Summary Session
Candice Roufosse
Maarten Naesens
Banff pre-meeting
Mission of Banff
Mission of Banff

• Banff classification is for biopsy-based DIAGNOSIS
  o For individual patient management
  o For clinical trials
    o Not a prognostic tool

• Needs to translate to patient benefit; Needs to be usable
  o Simplify and/or algorithms
  o Where possible, related to pathophysiology: that is what we want to target with treatments
visual assault

impossible not to make errors
A short survey on the Banff classification practice from Turkey

**Banff classification practice**
- Uses Banff criteria and includes scores in their report: 26 (84%)
- Uses Banff criteria but not include scores in their report: 5 (16%)

**Understands Banff classification**
- Completely: 16 (52%)
- Partially: 15 (48%)

n=31 respondents
Nephropathology WG
Foam Cell Arteriopathy:
No
Percent Luminal Narrowing:
20

Number (or estimate) of Arterioles
12

Arteriolitis:
No
Fibrinoid Necrosis:
No
Smooth Muscle Necrosis:
No
HUS Intimal Lesion:
No

Diagnosis Highlights:

KIDNEY ALLOGRAFT, LEFT, NEEDLE BIOPSY (INDICATION):
Biopsy Adequacy: Adequate

Category 3: Suspicious (Borderline) for Acute TCMR:
TCMR Borderline: Yes, Suspicious

Category 4: TCMR:

Chronic Active TCMR: IA

Chronic Changes:

Possible Evidence of Calcineurin Inhibitor Toxicity:
Yes; Evidence of Isometric Tubular Vacuolization

Errors and Warnings

Error: Type and extent of PTC inflammation must be specified when severity is positive
Rather than algorithms: a mandate for simplification!

- It should be universally applicable
  - Hierarchy in time and/or in availability in tests

<table>
<thead>
<tr>
<th>Morphological diagnosis</th>
<th>Diagnosis</th>
</tr>
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<tbody>
<tr>
<td>MVI</td>
<td>MVI, DSA+ = AMR</td>
</tr>
<tr>
<td></td>
<td>MVI, DSA- = cause unknown</td>
</tr>
</tbody>
</table>
The main clinical difficulty with BANFF CLASSIFICATION is in AB AMR category

\[ \text{ABMR} \quad \equiv \quad \text{MVI} \]

antibody mediated rejection

microvascular inflammation

Help clinicians to guide therapy?

We prefer to use

the term “microvascular inflammation”

with or without DSA,

instead of AMR
Consensus and changes to the classification
<table>
<thead>
<tr>
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<th>I</th>
<th>II</th>
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<th>IV</th>
<th>V</th>
<th>VI</th>
<th>VII</th>
<th>VIII</th>
<th>IX</th>
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<td></td>
<td></td>
</tr>
<tr>
<td>Change</td>
<td>n/a</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
</tbody>
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"The Banff classification is changing too often"
Rethinking the consensus process

- Evidence level: “at least 2 independent groups provide evidence”
- Banff consensus using KDIGO, DELPHI,…
Stress-testing the changes?

Simulating changes to the Banff classification before final implementation

Multicenter!
Innovation and the future
Banff Classification for Allograft Pathology is forward-looking

• Via Multi-disciplinary Working Groups
  o Pathologists, nephrologists, immunologists, computer/data scientists, tissue typers,…

• Conflict between innovation and regulation/implementation
The iBox roadmap

2012
- iBox project design

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2021
- Publication on dynamic iBox (Lancet Digital Health)
- First application of iBox (BMJ open): Transform Study
- eGFR trajectories (Kidney Int)

2022 - 2023
- iBox as a surrogate endpoint
- Qualification process iBox Clinical use: recruiting RCT

The Lancet Digital Health
ClinicalTrials.gov
How can Banff both encourage innovation and ensure a robust clinical diagnostic classification?
Transcriptomic analysis of kidney transplant biopsies
Banff pre-meeting: Molecular diagnosis - Invasive

- Molecular tests likely become companion tools for diagnosis soon
- Several groups presented equivocal cases “solved” with molecular diagnosis
Vienna Case #1

Post-Tx DSA negative

Tac (low), MMF, Steroid

Dialysis (continuous/intermittent)

Catecholamines

CRP ▲ (max 17 mg/dL)

Third kidney biopsy

Morphology
v₀, i₀, t₀

g₀, ptc₁, C4d₀

► no rejection treatment

Extensive AKI score

60% medulla
MVI in Early Post-Tx Allografts with DGF C4d Deposition (case 2)

- 42 year male; ESRD secondary to GN NYD
- DGF; allograft Bx at 9 days post-Tx
- Moderate ATN with regenerative changes
- Focal cortical ptc3 with mononuclear cells
- Focally prominent medullary vasa recta inflammation
- PTCs diffuse C4d + (C4d3) by IF; focal C4d+ by IHC
- Banff 2019 scores: g0, i0, ti0, t0, v0, ptc3
  cg0, mm0, ci0, ct0, i-IFTA 0, t-IFTA 0, cv1, ah0
- “highly suspicious for active ABMR”
MVI in Early Post-Tx Allografts with DGF C4d Deposition (case 2)

- Pre-Tx PRA 0%
- Negative for HLA class I and class II DSA pre-Tx and at time of biopsy
- AT1R Ab <10 both pre-Tx and at time of Bx
- Non-HLA Ab screen negative
- ABMR gene expression of 190; below threshold (<236) for “molecular ABMR” (NanoString 34-gene set, University of Alberta, Ben Adam & Michael Mengel)
Kidney biopsy

- ptc 2 g1 cg0 c4d0
- Aah2
- FIAT III
- No BKV nephropathy

DSA negative!!  AT1R Ab: 38 U/ml
## Gene expression based probabilities

### Diagnosis based probabilities (%):

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>SL.203</th>
<th>Normal range</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMR</td>
<td>99.0</td>
<td>3.7 - 24.6</td>
<td>very high probability</td>
</tr>
<tr>
<td>TCMR</td>
<td>25.1</td>
<td>8.2 - 31</td>
<td>moderate probability</td>
</tr>
<tr>
<td>ATI</td>
<td>34.7</td>
<td>0.1 - 0.7</td>
<td>moderate probability</td>
</tr>
<tr>
<td>IFTA</td>
<td>18.7</td>
<td>7.9 - 19.7</td>
<td>low probability</td>
</tr>
</tbody>
</table>

### Banff lesion based probabilities (%):

<table>
<thead>
<tr>
<th>Banff lesion</th>
<th>SL.203</th>
<th>Normal range</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>g &gt; 0</td>
<td>25.2</td>
<td>12.5 - 32.5</td>
<td>moderate probability</td>
</tr>
<tr>
<td>ptc &gt; 0</td>
<td>94.4</td>
<td>14.2 - 33.9</td>
<td>very high probability</td>
</tr>
<tr>
<td>cg &gt; 0</td>
<td>0.2</td>
<td>1 - 3.9</td>
<td>unlikely</td>
</tr>
<tr>
<td>i &gt; 1</td>
<td>34.7</td>
<td>8.6 - 28.3</td>
<td>moderate probability</td>
</tr>
<tr>
<td>t &gt; 1</td>
<td>60.0</td>
<td>14.7 - 40.1</td>
<td>moderate/high probability</td>
</tr>
<tr>
<td>iifta &gt; 0</td>
<td>77.2</td>
<td>15.3 - 48.9</td>
<td>high probability</td>
</tr>
<tr>
<td>v &gt; 0</td>
<td>36.2</td>
<td>1 - 6.6</td>
<td>moderate probability</td>
</tr>
<tr>
<td>cv &gt; 1</td>
<td>63.6</td>
<td>27.5 - 57.3</td>
<td>high probability</td>
</tr>
<tr>
<td>ci &gt; 1</td>
<td>95.3</td>
<td>15.5 - 44.7</td>
<td>very high probability</td>
</tr>
<tr>
<td>ct &gt; 1</td>
<td>95.8</td>
<td>13.5 - 43.3</td>
<td>very high probability</td>
</tr>
</tbody>
</table>
Principal Components Analysis (PCA) of molecular scores:

- PC1 43% of variance
- PC2 37% of variance

Pathway analysis

Cell type analysis
Banff pre-meeting: Molecular diagnosis - Invasive

- Defined classifiers with thresholds being tested for added value to diagnosis in a variety of situations
  - AMR
  - BL/TCMR

- Banff Molecular Working Group seeking how to integrate into the classification
  - Define COU
  - Regulatory approval!

- Morphological diagnosis
- Molecular Diagnosis
Chronic active TCMR
Chronicity in rejection and the i-IFTA challenge

• Universal agreement that i-IFTA is a feature of poor prognosis
• Threshold of prognostic value of i-IFTA may be too high
  o i-IFTA 1 and ti1 may have prognostic value

• Evidence for i-IFTA as a feature of chronic TCMR remains conflicting
  o Some groups showing evidence to support causality of TCMR in iIFTA, though not in all cases
  o Other groups showing more mixed picture
    • Molecular profile showing inactive inflammatory infiltrates and/or evidence of AMR (=non-specificity of i-IFTA)
    • Limited response to anti-TCMR therapies
caTCMR: still a difficult entity

- Unresolved issues
  - i-IFTA belongs only in the TCMR category? Stress-test
  - Could be a score independent of main diagnostic group (like v, cv)?
  - How/if to treat it
  - Borderline! Can CCTT criteria help? Molecular?

- TCMR working group: call to broaden group to include clinicians and work towards solving these questions

**WE WANT YOU!**
Keep it as it is since 2019

Tubulitis is scored in all but severely atrophic tubules

- t in areas of preserved cortex
- t-IFTA in areas of IF (which in practice is mostly in mildly-moderately atrophic tubules).

<table>
<thead>
<tr>
<th>cortex/tubules</th>
<th>Normal</th>
<th>Mildly atrophic</th>
<th>Moderately atrophic</th>
<th>Severely atrophic</th>
</tr>
</thead>
<tbody>
<tr>
<td>No IF</td>
<td>t</td>
<td>t</td>
<td>t</td>
<td>-</td>
</tr>
<tr>
<td>IF</td>
<td>t-IFTA</td>
<td>t-IFTA</td>
<td>t-IFTA</td>
<td>-</td>
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**PROs:**
No new change
No need to evaluate the size of tubules
Will allow to compare the impact of « t » in IF and « t » in preserved areas in future studies

**CONS:**
Big change compared to 2017 and before, so no consistency between studies before and after 2017
Incorrect registry data before 2017 and any prognostic scores generated with the version of t prior to 2017
Banff and clinical trial design
Banff and clinical trial design

• Banff classification is not only used clinically, but also for clinical trials:
  o As endpoint (BPAR)
  o For inclusion

• Problem: most clinical trials (e.g. in AMR) use derivatives (keeping certain aspects but not all) and (much) older versions of the Banff classification

• Consensus to **not have separate Banff classifications** for clinical use and for use in trials

-> Mission to make Banff great again (for clinical trials)
Paths towards reinstalling the consensus Banff classification as standard for clinical trials

1. Simplify the classification for MVI/AMR
   - Reduce the footnotes
   - Clear definition of DSA+AMR vs. DSA-MVI (see next)

1. Define in the classification what is substantiated by evidence and clinically available, and what is not (yet)

3. Use algorithms, based on lesion scores, that automate and standardize the final diagnosis
   - The Paris system for automated Banff scoring
   - The Pittsburgh system for automated Banff scoring
   - Integration of both systems?
Paths towards reinstalling the consensus Banff classification as standard for clinical trials

4. Clinical trial design is hampered by current lowly reproducible discontinuous scoring
   - Morphometry might help, algorithms are being developed

5. Central pathology with clinical information provided to pathologists improves the accuracy

6. Move away from using BPAR as endpoint, but differentiate between TCMR and AMR, and take the difference into account in clinical trial design

7. Involve Banff community and pathologists in the international consensus on clinical trial design and endpoints, example of the TTS-ESOT-ATS-Banff TCMR Working Group
Surrogate endpoints for late graft failure may have to take into account the multiple factors acting together.
Let’s celebrate the success story of the iBox

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- Qualification process
- iBox as a surrogate endpoint
- External validation cohort & RCTs data acquisition
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2022 - 2023
- iBox Clinical use: recruiting RCT
- Transplant societies endorsement (TTS, ESOT, AST)
Let’s celebrate the success story of the iBox and the closing of the Banff surrogate endpoints WG.
AMR and MVI
The Banff schema overly simplifies the full spectrum of anti-HLA DSA associated AMR

```
<table>
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<tr>
<th>Clinical setting</th>
<th>Early acute ABMR (+XM)</th>
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<td></td>
<td>Clinically apparent: AKI, &lt;1 month post-transplant</td>
<td>Usually clinically apparent: AKI</td>
<td>Subclinical</td>
<td>Subclinical or clinically apparent: Progressive renal insufficiency, proteinuria, hypertension</td>
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<td>History</td>
<td>ATN, thrombi, mild capillaritis, v lesions</td>
<td>ATN, thrombi, capillaritis, v lesions</td>
<td>Capillaritis only (g, ptc)</td>
<td>Capillaritis and TG, TA, or PTCBMMML</td>
</tr>
<tr>
<td>C4d</td>
<td>Diffuse +</td>
<td>+</td>
<td>Negative, focal +, occasionally diffuse +</td>
<td>Negative, focal +, occasionally diffuse +</td>
</tr>
<tr>
<td>Serum DSA</td>
<td>High</td>
<td>High</td>
<td>Low, mid</td>
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“Need to recognize exceptions”
The Banff schema overly simplifies the full spectrum of anti-HLA DSA associated AMR

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<td>Low, mid</td>
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The Banff schema overly simplifies the full spectrum of HLA DSA positive MVI = AMR

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<th>C4d</th>
<th>Serum DSA</th>
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<td></td>
<td></td>
<td></td>
<td>High</td>
</tr>
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</table>

& disease independent?
Definition of HLA-DSA
- Technical hurdles
- STAR guidance
- AMR Working Group

MVI triggers interaction with HLA lab

Non-HLA antibodies
- allo-immune?
- auto-immune?

STAR review

NK cells
- Missing self
- Other activation mechanisms

Ischemia reperfusion injury
Different types of infiltrates?

Tools needed

Validation needed

Validation needed
Not considered as sABMR or ABMR in any Banff update
n=3171

Banff'01

- ABMR n=74
- sABMR n=238
- No ABMR n=179

Banff'13

- ABMR n=199
- sABMR n=292
- No ABMR n=292

- DSA+ C4d- MVI+
- DSA+ C4d+ MVI+
- DSA-C4d+ 1st+ MVI+

Banff’17

- ABMR n=237
- No ABMR n=254
- DSA+ C4d- MVI+
- DSA- C4d+ MVI+
- Isolated ptc

New ‘22 proposal

- HLA-DSA pos, AMR
- MVI
- C4d+
- HLA-DSA-neg
- MVI, cause unclear (non-HLA?, missing self?, IRI? …)

No ABMR (DSA+)
Options for a definition of “DSA-negative MVI”

**Microvascular inflammation** needs to be defined

- **g + ptc ≥ 2**

- **Aligned with Banff for AMR: 1\textsuperscript{st} + 2\textsuperscript{nd} Banff criterion:**
  1. Histologic evidence of acute tissue injury, including 1 or more of the following: • Microvascular inflammation (g > 0 and/or ptc > 0), in the absence of recurrent or de novo glomerulonephritis, although in the presence of acute TCMR, borderline infiltrate, or infection, ptc ≥ 1 alone is not sufficient and g must be ≥ 1 • Intimal or transmural arteritis (v > 0) • Acute thrombotic microangiopathy, in the absence of any other cause • Acute tubular injury, in the absence of any other apparent cause
  2. Evidence of current/recent antibody interaction with vascular endothelium, including 1 or more of the following: • Linear C4d staining in peritubular capillaries or medullary vasa recta (C4d2 or C4d3 by IF on frozen sections, or C4d > 0 by IHC on paraffin sections) • At least moderate microvascular inflammation ([g + ptc] ≥2) in the absence of recurrent or de novo glomerulonephritis, although in the presence of acute TCMR, borderline infiltrate, or infection, ptc ≥ 2 alone is not sufficient and g must be ≥1

- **Restricted definition of MVI*: g+ptc ≥ 2, in the absence of glomerulonephritis, with g > 0 in the presence of TCMR or borderline changes

- **Other option?**

*Senev et al AJT 2018: 97% overlap

#Irrespective of concomitant TCMR
*Roufosse et al Transplant Int 2022
Ptc working group

- Banff ptc score: first discussion 2003 and 2005, included in Banff 2007
- Current ptc score related to the number of cells in the most affected ptc
- Single-center data suggest that ptc extent could be relevant in addition to the current ptc score
- Primary aim of the WG: evaluate in multicenter evaluation whether the ptc score + ptc extent are more relevant than ptc score alone
- Question of the relevance of dilatation of the ptc and other questions to be answered
- Currently setting up the DTA, distribution of samples, etc.
Digital pathology
Banff Digital Pathology Working Group

IMAGE BANK(S) / COLLECTION(S)
PLATFORM TO SHARE ALGORITHM(S)
COMPETITION(S)/TRIAL(S)


Pilot Image Bank: DPLab
https://dplab.gsu.edu/

@banffdpwg YouTube

Radboudumc Diagnostic Image Analysis Group/DIAGGRAFT Study

Dr. Renate Kain on the “Big Picture”
Dr. Richard Levenson on novel microscopy
Dr. Peter Boor on their server
Dr. Laura Barisoni and their group’s peritubular capillary, glomerular, & other algorithms
Dr. Ul Balis on his novel image analysis tool
Dr. Lynn Cornell on immunofluorescence scanners

https://www.computationalpathologygroup.eu/projects/diaggraft/
Xenotransplantation

• Pre-clinical models
  o pig to primate
  o GTKO pig to primate
  o TKO pig to primate

• Early (time post-transplant) observations in humans (pig to human decedent) mirror primate observations

• Molecular diagnosis: “B-POT” – first cross-species gene expression panel
# Proposal for Banff scoring for xenografts

## Thrombotic microangiopathy scoring

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>glomeruli</td>
<td>gTMA</td>
<td>no thrombi</td>
<td>≤25%</td>
<td>26–50%</td>
</tr>
<tr>
<td>arteriolar</td>
<td>aTMA</td>
<td>no thrombi</td>
<td>≤25%</td>
<td>26–50%</td>
</tr>
</tbody>
</table>

## C4d scoring

<table>
<thead>
<tr>
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<th>0</th>
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<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>glomeruli</td>
<td>gC4d</td>
<td>no staining</td>
<td>≤25%</td>
<td>26–50%</td>
</tr>
<tr>
<td>vascular</td>
<td>vC4d*</td>
<td>no staining</td>
<td>≤25%</td>
<td>26–50%</td>
</tr>
</tbody>
</table>

*arteries and arterioles
Working groups

- PTC, sensitised, TCMR, digital, non-invasive diagnostics, molecular, Rules and dissemination presented
- EM WG met
- HIV, TMA, recurrent glomerular disease sent in reports

- Implantation biopsy WG may be revived
- Activity and chronicity indices WG
- Xenotransplantation WG
Thank you very much for all your hard work