Banff Pancreas Session Summary

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ITAC, Buenos Aires

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Sao Paulo Brazil

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Universita di Pisa, Italy
Banff Pancreas Session Summary

Cinthia B. Drachenberg, M.D.

1st Pancreas discussions in 1995 Banff meeting
EVALUATION OF PANCREAS TRANSPLANT NEEDLE BIOPSY
Reproducibility and Revision of Histologic Grading System

Drachenberg, Cinthia B.¹; Papadimitriou, John C.¹; Klassen, David K.²; Racusen, Lorraine C.³; Hoehn-Saric, Edward W.²; Weir, Matthew R.²; Kuo, Paul C.⁴; Schweitzer, Eugene J.⁴; Johnson, Lynt B.⁴; Bartlett, Stephen T.⁴,⁵

Author Information

Transplantation: June 15, 1997 - Volume 63 - Issue 11 - p 1579-1586
2008 TCMR and graft sclerosis/chronic rejection guidelines

2011 ABMR rejection guidelines
Treatment of Rejection – Consensus Conference Statements

First World Consensus Conference on Pancreas Transplantation

Pisa, Italy, October 2019

Dr. Ugo Boggi
Clinico – Pathological Correlations of Pancreas Allograft Biopsies

Canadian Society of Transplantation
and Banff Foundation for Allograft Pathology Joint Meeting
September 2022

Jon S. Odorico, MD, FACS, FAST
Professor of Surgery
Division of Transplantation
Director, Pancreas and Islet Transplantation
The Presence of Donor-specific Antibodies Around the Time of Pancreas Graft Biopsy With Rejection Is Associated With an Increased Risk of Graft Failure

Sandesh Parajuli, MD,1 Arjang Djamali, MD,1,2 Didier Mandelbrot, MD,1 Fahad Aziz, MD,1 Nancy Radke, RN,2 Dixon Kaufman, MD, PhD,2 and Jon Odorico, MD2

![Graph showing survival probability over months post index biopsy with different groups labeled Rej/DSA-, Rej+/DSA-, Rej+/DSA+, and Rej/+DSA+ with a P-value of 0.11.]
How Should Pancreas Transplant Rejection Be Treated?

Fahad Aziz, MD,† Sandesh Parajuli, MD,† Salah Uddin, MD,† Kylie Harrold, PA,‡ Arjang Djamali, MD,†,‡ Brad Astor, PhD,† Jon Odorico, MD,‡ and Didier Mandelbrot, MD†

158 first BPAR episodes
1997-2016
54% SPK, 28% PTA, 18% PAK
Graded by Banff 2011 criteria
C4d staining was introduced in 2006
GR1 – 47%
GR2 – 30%
GR3 - 23%

Responded to Steroids alone
• 83% Gr1
• 60% Gr2
• 33% Gr 3

Responded to Steroids + ATG
• 69% Gr1
• 76% Gr2
• 73% Gr 3

Aziz et al. Transplantation 2019, 103: 1928-34
How Should Pancreas Transplant Rejection Be Treated?

Fahad Aziz, MD,1 Sandesh Parajuli, MD, Salah Uddin, MD,1 Kylie Harrold, PA,1 Arjang Djamali, MD,1,2 Brad Astor, PhD,1 Jon Odorico, MD,2 and Didier Mandelbrot, MD1

Graft Survival with steroids alone vs. steroids + ATG

Grade 1

Grade 2

Grade 3

A

B

C

P = 0.3253

P = 0.0256

P < 0.0001

Aziz et al. Transplantation 2019, 103: 1928-34
UW Wisconsin Algorithm for Treatment of Pancreas Graft Rejection (depending on biopsy findings)

Increased Enzymes

<table>
<thead>
<tr>
<th>H&amp;E</th>
<th>C4d</th>
<th>DSA</th>
<th>Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neg</td>
<td>Neg</td>
<td>Neg</td>
<td>Look for other cause</td>
</tr>
<tr>
<td>Neg</td>
<td>Neg</td>
<td>Neg</td>
<td>CS</td>
</tr>
</tbody>
</table>

- Indeter: Neg or Indeter
- Gr. I: Neg
- Gr. II-III: Neg

- Focal or Diffuse
  - +/- DSA
  - CS + PP/IVlg
  - +/- Ritux
  - +/- Bortez
  - CS/Thymo

CS = corticosteroid bolus and taper
PANCREAS BIOPSIES: CLINICAL-BIOPSY CORRELATIONS

Pablo Daniel Uva
INSTITUTO DE TRASPLANTES Y ALTA COMPLEJIDAD (ITAC – NEPHROLOGY)
Buenos Aires, Argentina
SURROGATE MARKERS

- **Kidney dysfunction (Cr/proteinuria) - Kidney biopsies (limited to SPK)**
  - Synchronic biopsy studies at pancreas dysfunction:
  - Biopsy proven kidney rejection:
    - Sensitivity: 60%
    - Specificity: 70%

- 101 concurrent K/P bx @ dysfunction:
  - 47 kidney, 31 pancreas and 23 E
  - Concordant rejection (40%)
    - 57% different types/grades

Graft dysfunction in SPK transplantation: Results of concurrent pancreas and kidney biopies. Uva et al. AJT 2019
Biopsies at early relaparotomy

- 182 consecutive transplant performed 2012-2019
- 51 pt biopsied at time of relaparotomy during 1st mo (without dysfunction)
- Subclinical rejection found 22%
  - 1 Kidney only, 6 pancreas only, 4 both grafts
OUTCOMES: Experience with Duodenal Graft Biopsy

134 Duodenal graft biopsies
52 patients (39 PAK, 9 PTA, 6 SPK, 1 SPLK)

87 Protocol
- Normal: 75 (86%)
- Duodenitis: 4
- Minimal Inflamm: 3
- CMV: 3
- Rejection: 1 (1.1%)
- Congestion: 1

38 Disfunctions
- Normal: 19 (50%)
- Minimal Inflamm: 5
- Duodenitis: 4
  - Mild: 1
  - Severe/Ulcers: 3
- CMV: 2
- Rejection: 7 (18%)

9 Others
- Normal: 3
- Minimal Inflamm: 3
- CMV: 2
- Duodenitis: 1
Correlation between Duodenal and Pancreas Graft Biopsy (N = 23)
Concordance: 16 (70%)

<table>
<thead>
<tr>
<th>DUODENAL BIOPSY</th>
<th>PANCREATIC BIOPSY</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Normal</td>
<td>6</td>
</tr>
<tr>
<td>Rejection</td>
<td>Rejection</td>
<td>7</td>
</tr>
<tr>
<td>- Mild</td>
<td>- Moderate</td>
<td>1</td>
</tr>
<tr>
<td>- Moderate</td>
<td>- Mild</td>
<td>1</td>
</tr>
<tr>
<td>- Moderate</td>
<td>- Moderate</td>
<td>2</td>
</tr>
<tr>
<td>- Moderate/Severe</td>
<td>- Severe</td>
<td>1</td>
</tr>
<tr>
<td>- Moderate/Fibrosis</td>
<td>- Fibrosis</td>
<td>1</td>
</tr>
<tr>
<td>- Severe</td>
<td>- Mild</td>
<td>1</td>
</tr>
<tr>
<td>Duodenitis</td>
<td>Normal/indet.</td>
<td>2</td>
</tr>
<tr>
<td>Ulcer</td>
<td>Normal</td>
<td>1</td>
</tr>
</tbody>
</table>
CONCLUSIONS AND FUTURE PERSPECTIVES

- Most patients are C4d and DSA negative; Solitary PT presented higher prevalence of patients C4d+ and DSA+
- Solitary PT are more likely to present more severe acute rejections, ABMR and fibrosis;
- SPK and Solitary PT rejections were predominantly treated with Thymoglobulin and the latter required PP and IVIG more frequently;
- De novo DSA+ Solitary PT presented higher rate of immunological graft loss (OR: 5.07);
- Protocol duodenal graft biopsies do not seem to be a reliable surrogate marker alone for pancreatic rejection;
- Duodenal graft biopsies can achieve good correlation (70%) with pancreatic biopsies in cases with disfunction;
2022 Banff-CST Joint Meeting

September 19 - 23, 2022
Banff Centre for Arts and Creativity
Banff, Alberta

Organized by
Banff Foundation
for Allograft Immunology
Non-invasive tools for the diagnosis of pancreas rejection

Pedro Ventura-Aguiar

Nephrology and Kidney Transplant Department
Hospital Clinic Barcelona
pventura@clinic.cat

@Pventura_Aguiar  Pedro_Aguiar7
Non-invasive tools for the diagnosis of pancreas graft rejection

**DSA**
- DSA’s are associated with increased risk of graft rejection, even in the absence of graft dysfunction
- DSA’s are not patognomonic of graft rejection
  - Up to 50% of patients with DSA+ and no histological evidence of graft rejection

**Donor-derived cell-free DNA (dd-cfDNA)**
- Presented a good negative predictive (NPV – 93%) value in a biopsy-matched cohort (N= 41)
- Outperforms lipase for the diagnosis of acute rejection
  - Lipase: AUC 0.74
  - Dd-cfDNA: ACU 0.89
- May correlate with DSA (despite absence of ABR)
Non-invasive tools for the diagnosis of pancreas graft rejection

Donor-derived cell-free DNA (dd-cfDNA)
- Presented a good negative predictive (NPV – 93%) value in a biopsy-matched cohort (N=41)
- Outperforms lipase for the diagnosis of acute rejection
  - Lipase: AUC 0.74
  - Dd-cfDNA: ACU 0.89
- Elevates early in the post-transplant (1h), and decrease thereafter (24h -> 1month). Stable values >3months
- Differential expression of dd-cfDNA between transplant type - SPK vs PTA
  - Both in the presence and absence of rejection/inflammation

Plasma gene expression profiling
- Fairly good negative predictive value (NPV – 86.7%) and specificity (83.3%)
- Increased OR for the diagnosis of acute rejection compared to lipase
  - Lipase: OR 1.010 (95% CI 1.002-1.018)
  - Trugraf: OR: 5.8 (95% CI 2.10-16.5)

Peripheral blood immune phenotyping
- Pre-transplant CD3+ cells >6% increased risk for early AR >15x
- May provide insight to patients at risk for early acute rejection
  - Tailoring immunosuppression?

Yoo A, Bromberg JS, Scalea JR et al – Unpublished (manuscript under revision)
Williams MD et al – Transplantation Direct 2022;8: e1321
Non-invasive tools for the diagnosis of pancreas graft rejection

Future perspectives

• **Dd-cfDNA** and **plasma gene expression**
  - Large multicenter clinical trials to validate clinical utility of dd-cfDNA in pancreas transplantation
  - Correlation between DSA+ and graft injury
  - Correlation with histological severity and response to treatment
  - Influence on patient management (i.e. reduce need for protocol biopsy in DSA+ patients)
  - Correlate with long-term graft survival

• **Peripheral blood immune profiling**
  - Characterize correlation with disease severity, prognostic ability, and clinical validity

• **Eplet mismatch** to predict risk for pancreas graft rejection, dnDSA formation, and graft survival

• **cfDNA organ/cell specific methylation profiles** for the diagnosis of acute rejection

• **Imaging enhanced techniques** for the diagnosis of pancreas acute rejection
  - ultrasound – CEUS/ARFI;
  - CT scan – PET
Pancreas Transplant Rejection: RNA sequencing Analysis

Surya V Seshan
Pathology & Laboratory Medicine
Muthukumar Thangamani
Division of Nephrology and Transplantation
Weill Cornell Medicine
New York – Presbyterian Medical Center
New York

Banff Transplant Pathology-CST 2022 – Pancreas transplant session
Messenger RNA and MicroRNA Transcriptome Profiling: A Valuable Tool to Study Allograft status

Analysis of graft tissue-mRNA transcriptome

Assessing the status of innate immune mechanisms of graft

- Cell type enrichment analysis-infiltrating, native/resident cells
- Complement components
- Chemokines, cytokines, INF, caspases
- Pattern recognition receptors
- Damage-associated molecular pattern
- Metabolic pathways – Endoplasmic oxidative pathways, mitochondrial stress

Mueller F et al, JCI insights, 2019
Differential Gene Expression Analysis in Pancreas Tx

Volcano plot showing the log2 fold change and -log p-value of differentially expressed genes between rejection and normal.

232 differentially expressed (P value < 0.05, log2 fold change >1)
2022 Banff-CST Joint Meeting
SEPTEMBER 19 - 23, 2022
BANFF CENTRE FOR ARTS AND CREATIVITY
BANFF, ALBERTA
ORGANIZED BY
Technical failure versus acute rejection: Histological studies

Catherine Horsfield
Guy’s & St Thomas’ NHS FT
London, UK
• January 2009-2016, 198 transplant pancreas implants;
  • SPK – 180; PTA – 6; PAK – 12
  • >75% white; 46% female; donor age 23 – 45

• 23 explants for ‘technical failure’ grafts lost within 90 days.
  • SPK – 20; PTA – 2; PAK – 1
  • 19 of the 23 were explanted within 4 weeks;
  • Risk for loss:
    • more likely in non-white recipients; older donor.
    • other parameters were not significant in this cohort (eg cold ischaemic time).
• Review of pathological findings in the 23 pancreatectomies;

• Review of clinical data and indication for transplant pancreatectomy:
  • Including retrospective review of case notes, serology including white cell counts, CRP, amylase, creatinine, Tacrolimus levels, imaging, intra-operative findings, discharge summaries, team meeting documentation to assess for likelihood of rejection

• Histological review:-
  9 of 23 explants for technical failure showed morphological features of rejection:
  a. 5/10 cases with duodenal leak clinically showed ATCMR and 2 of these were suspicious for AMR;
  b. 4/5 cases with peripancreatic collections clinically showed ATCMR and 2 of these were suspicious for AMR;
  c. 0/7 cases with massive thrombosis clinically showed rejection
In summary

• Clear evidence that Technical Failure should not be used as a blanket clinical term for all graft loss within 90 days of transplantation;

• Correlation between perceived clinical cause of early graft loss and pathological diagnosis is poor and/or might be multifactorial;

• Thorough histological examination, ideally with DSA data, will potentially confirm the cause of transplant loss, up to a third of which might include features of rejection;

• Clinical features of a thrombotic process do not exclude rejection, in fact most cases of rejection will have elements of a thrombotic process;

• **Potential prognostic implications in defining precise cause of graft loss: early loss of transplant pancreas due to antibody mediated rejection is associated with loss of kidney through AMR within 1 year.**
PANCREAS TRANSPLANT BIOPSIES

CLINICO-PATHOLOGICAL CORRELATIONS THROUGH THE ERAS SPANNING TWO DECADES

A. Mikhailov
Department of Pathology
Wake Forest School of Medicine
Winston-Salem, NC
WFBMC 2001-2022:
22 Simultaneous Pancreas and Kidney Histological Specimens Acquired

<table>
<thead>
<tr>
<th>Kidney Rejection</th>
<th>Pancreas Rejection</th>
<th>No Pancreas Rejection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney Rejection</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>No Kidney Rejection</td>
<td>6</td>
<td>11</td>
</tr>
</tbody>
</table>

Pancreas rejection ACMR grade 1 to 3
Kidney rejection Banff borderline to 1B

*Concordance rate: 14/22 = 64%
WFBMC 2001-2022: Donor specific antibodies are seen more often in patients with severe ACMR, and especially with repeated ACMR

<table>
<thead>
<tr>
<th></th>
<th>DSA</th>
<th>Preformed DSA</th>
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<tbody>
<tr>
<td>No rejection</td>
<td>35.3%</td>
<td>22.4%</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>20.8%</td>
<td>16.7%</td>
</tr>
<tr>
<td>ACMR 1</td>
<td>30.8%</td>
<td>18.5%</td>
</tr>
<tr>
<td>ACMR 2</td>
<td>38.5%</td>
<td>26.9%</td>
</tr>
<tr>
<td>ACMR 3</td>
<td>56.3%</td>
<td>12.5%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>No rejection</th>
<th>Single episode of ACMR</th>
<th>Multiple episodes of ACMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive DSA</td>
<td>14%</td>
<td>27%</td>
<td>63%</td>
</tr>
<tr>
<td>Preformed DSA</td>
<td>7%</td>
<td>20%</td>
<td>36%</td>
</tr>
</tbody>
</table>
A systematic approach and use of CD3 and CD68 enhances diagnostic yield in pancreas allograft biopsies

John C. Papadimitriou, M.D., Ph.D.
Professor of Pathology
University of Maryland School of Medicine
Patient information : 97 pancreas tx bx

- 53 pt, 55 allografts, 30 SPK, 14 PAK (2 regrafts), 11 PTA
- 29 males, 24 females
- Age 21-65 (average 43)
- 1-7 biopsies per patient
- Patients were followed for mean 3.3y post biopsy (1 d to 18y) and mean of 6.2y post tx (range is 12 d to 23 years).

- 14 (25.4%) patients lost their graft during the study period at a mean time of 4.5y post bx and 11.5y post tx.
CD3, CD68 and CD20 **septa and acini separately**

Semiquantitative evaluation

0= negative or negligible (baseline)
1= above baseline but still sparse,
2= multifocal, larger aggregates but ≥50% areas free of positive staining infiltrates
3= Diffuse, multifocal, confluent but ≤50% areas free of positive staining infiltrates

**To define the baseline:** 4 protocol, 4 pre-implantation and 4 normal areas in native pancreatectomies.
AMR

- Classic AMR (acute and chronic, mixed) (8)
- No AMR
- C4d or DSA only (4)
OVERALL IMPACT OF CD3 AND CD68 ACINAR INFLAMMATION

CD3 ACINAR

Kaplan-Meier survival estimates

P < 0.0001

CD68 ACINAR

Kaplan-Meier survival estimates

P < 0.0001
OVERALL IMPACT OF CD3 AND CD68 SEPTAL INFLAMMATION

CD3 SEPTAL

Kaplan-Meier survival estimates

- c3septal = 0
- c3septal = 1
- c3septal = 2
- c3septal = 3

P = 0.0033

CD68 SEPTAL

Kaplan-Meier survival estimates

- cd68sep = 0
- cd68sep = 1
- cd68sep = 2
- cd68sep = 3

P < 0.0001
Impact of CD3 and CD68 in diagnosis

Total 97 biopsies

a) 46 biopsies (47.4%): minimal or no impact (same diagnosis as H&E)
   78% no rejection

b) 45 biopsies (46.3%): helpful confirmatory or clarification of difficult diagnosis
   80% rejection (p <0.0001, comparison between a and b)

c) 6 biopsies (6%): upgrade of rejection grade (2 Banff I to II, 4 Indeterminate to Banff I)
Value of immunostains

• Increase sensitivity for diagnosis
• Contribution to accurate Banff grading
• Elucidate treatment effect
• Help in the differentiation between rejection and non-rejection processes
Treatment effect in TCMR: Comparison between rejection diagnostic biopsy and 3 week biopsy post treatment (n=8)

<table>
<thead>
<tr>
<th></th>
<th>Pre-treatment vs</th>
<th>Post –treatment</th>
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<tbody>
<tr>
<td>CD3 Septal</td>
<td>p=0.05</td>
<td></td>
</tr>
<tr>
<td>CD3 Acinar</td>
<td>p=0.027</td>
<td></td>
</tr>
<tr>
<td>CD68 Septal</td>
<td>p=NS</td>
<td></td>
</tr>
<tr>
<td>CD68 Acinar</td>
<td>p=NS</td>
<td></td>
</tr>
</tbody>
</table>
Before Tx

After Tx

CD3

CD68
CD3  Before Tx  After Tx

No significant response
Conclusions

1. The existing Banff guidelines for grading perform well as expected. (There was highly statistically correlation between Banff grades of rejection and graft loss.)

2. The addition of CD3 and CD68 immunostains is helpful in ambiguous cases, and helps in the differentiation of non-rejection related processes.
Diagnosis of non-rejection related processes in pancreas transplant biopsies

Cinthia B. Drachenberg, M.D.
Professor of Pathology
University of Maryland School of Medicine
TCMR

![Bar chart showing different categories and their respective mean values. The chart includes legend labels for mean of c3septal, mean of c3acinaria, mean of cd68sep, and mean of cd68aci.]
Suspected drainage impairment: Periductal fibrosis
Distinction between exocrine non-rejection pathologies and acute rejection

4  Ductal (drainage issues)
8  Post surgical peripancreatic reaction/infection/ischemic pancreatitis

CD3 septal and acinar and CD68 septal and acinar NS between these groups

Compared with
26 mild TCMR (Banff I)

CD3 septal  p .00004
CD3 acinar  p .00008

CD68 septal  p NS
CD68 acinar  p NS
Non rejection related pathology found in 15 of 97 biopsies (15.5%)

- Non-rejection processes can be confused clinically with acute rejection when there are abnormal enzymes.

- Application of the Banff rejection schema and use of other histological features are useful for diagnosis, however, the use of CD3 /CD68 stains, mainly to demonstrate absence of acinar CD3 is very helpful in ambiguous cases.
Currently the Banff pancreas working group is preparing a comprehensive multidisciplinary report for publication, to disseminate recent advances in pancreas allograft pathology.