

## CHAPTER 6.3 Histopathological classification of transplant rejection according to Banff

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### 1 Introduction

The Banff Classification of Renal Allograft Nephropathy is the result of a consensus process managed by the Banff Foundation ([www.banfffoundation.org](http://www.banfffoundation.org); last accessed December 2024). This started in 1991 with an expert meeting in Banff, Canada; the results of these biannual meetings have been published in more than a dozen manuscripts. The latest iteration is based on the 2022 meeting held in Banff again [1]. As the only such project after termination of the Cooperative Clinical Trials in Transplantation (CCTT) Classification [2], the Banff Classification has become the dominant classification scheme for kidney allograft pathology for clinical practice, scientific and pharmaceutical trials. Unfortunately, the high expectations for such a classification regarding transparency, clarity and practical applicability have not always been met. Currently, the entire up-to-date content of the Banff Classification can be found on the Banff Foundation's website (<https://banfffoundation.org/central-repository-for-banff-classification-resources-3/>; last accessed December 2024). The following sections provide a guide to the general principles and implementation of the Banff Classification in its most recent form. We refrain from copying the most recent iteration, as this would quickly become outdated. Instead, we encourage the users of this manual to consult the Banff website. The Banff Classification in their most recent iteration should be implemented by transplant centres in a consensus between clinicians, nephropathologists and immunogeneticists under consideration of local resources. Individual patients and their biopsies are not always best served by rigorous adherence to the Banff Classification. Instead other available evidence and reason will provide additional guidance in the interdisciplinary diagnostic process.

## 2 General principles of the Banff Classification of renal allograft pathology

The content of the Banff Classification can be divided into four parts: Banff Definitions, Banff Lesion Scores, Additional Diagnostic Parameters (ADPs) and Banff Diagnostic Categories and Subcategories. Throughout this text, all official Banff terms will be given in capitals. The best-known parts of the Banff Classification are the Banff Lesion Scores, e.g., Banff t for tubulitis, g for glomerulitis. These are all histopathological descriptors on an ordinal scale of 0, 1, 2, 3, where 0 is usually denoting absence and 3 a severe finding. Note that severity can be graded in an individual tissue compartment, as in t for tubulitis or cg for transplant glomerulopathy, where the most severely affected tubule or glomerulus would dictate the score. For other Lesion Scores it is graded as the extent of involvement, as in the Banff Lesion Score g for transplant glomerulitis. Again, the reader is referred to the Banff website for the most recent overview of these Lesion Scores.

Overlooked until the review published in 2018 were the Additional Diagnostic Parameters (ADPs). ADPs have been around since the beginning. They are, with the exception of “C4d Staining On Fresh-Frozen Or Paraffin-Embedded Tissue”, binary (yes or no, absent or present) defined by the non-Lesion Score nodes in the Banff Classification decision tree to reach all Diagnostic Categories. They refer not only to histopathology, as in “Absence Of Recurrent Or De Novo Glomerulonephritis”, but also to other diagnostic disciplines, as in “Prior Evidence Of Donor-Specific Antibody”. The Banff definitions underpin the other components of the Banff Classification. To define endarteritis for the Banff Lesion Score v, Banff provides a definition of “artery” as opposed to arterioles. Finally, the Banff Classification provides diagnostic categories and subcategories. With some minor changes in Banff 2019 that were quickly reversed, these categories are the following for the 2022 iteration [1]:

**Table 1** Banff Diagnostic Categories

Banff Diagnostic Categories	Banff Diagnostic Subcategories
1. Normal biopsy or nonspecific changes	None
2. Antibody-mediated rejection and microvascular inflammation/injury (AMR/MVI)	Active AMR, chronic AMR, chronic-active AMR, C4d-staining without evidence of rejection, microvascular inflammation/injury (MVI), DSA-negative and C4d-negative, probable AMR; C4d staining with acute tubular injury (ATI)
3. Suspicious (borderline) for acute T cell-mediated rejection (TCMR)	None
4. T cell-mediated rejection (TCMR)	Acute TCMR IA, IB, IIA, IIB, III Chronic-active TCMR IA, IB, II
5. Interstitial fibrosis and tubular atrophy	Grade I (mild), grade II (moderate), grade III (severe)
6. Other changes not considered to be caused by acute or chronic rejection	Polyomavirus nephropathy, post-transplant lymphoproliferative disorder, calcineurin inhibitor toxicity, acute tubular injury, recurrent disease, de novo glomerulopathy (other than transplant glomerulopathy), pyelonephritis, drug-induced interstitial nephritis

Modified from (<https://banfffoundation.org/central-repository-for-banff-classification-resources-3/>; last accessed December 2022)

Obviously, Category 5 is not a diagnosis *per se*. It grades interstitial fibrosis and tubular atrophy of the cortex (as codified in the Banff Lesion Scores ci and ct) into the usual ordinal scale of absent, mild (Grade I), moderate (Grade II) and severe (Grade III). While Category 1 is mutually exclusive with Categories 2, 3, 4 and 6, and Category 3 is mutually exclusive with Category 4, all other Categories may coexist in a summary Banff diagnosis. For example, a biopsy could show chronic-active antibody-mediated rejection (caAMR) from Category 2, acute T cell-mediated rejection IIA from Category 4, moderate IFTA from Category 5

and a diagnosis of recurrent IgA glomerulonephritis from Category 6. Indeed, several diagnoses from Category 6 may co-exist.

### **3 Banff Diagnostic Category 2: Antibody-mediated rejection and microvascular inflammation/injury (AMR/MVI)**

In line with the rapidly accumulating and evolving understanding of AMR over the years, Category 2 has undergone by far the most changes of all diagnostic categories in the Banff Classification. A concise review of these changes prior to 2017 can be found elsewhere [3, 4]. Considering the new subcategories added in 2022 Microvascular Inflammation/Injury (MVI), DSA-Negative And C4d-Negative, Probable AMR, C4d Staining With Acute Tubular Injury (ATI), it is important not to interpret them as *bona fide*, true AMR. Rather, they should be considered as provisional subcategories with unknown clinical implications. Similarly, at the time of writing, “Probable AMR” should not AMR proper or a mild form of AMR, but rather a subcategory of unknown diagnostic and therapeutic significance. It is clear that the focus of the Banff Classification is not to be a tool for clinical practice and pharmaceutical trials, but rather to drive research that may or may not provide the evidence for such novel diagnostic subcategories. This ignores the needs of both clinicians and pharmaceutical researchers who require internationally recognised, evidence-based diagnostic definitions. This gap has been filled by a critical review of the evidence base of AMR-relevant Banff Lesion Scores, ADPs and Category 2 diagnoses on behalf of the European Society of Organ Transplantation and the European Medicines Agency, which consolidates the evidence-based core consensus definitions of AMR diagnostic categories and may also serve as a useful reference point for daily clinical practice [4].

### **4 Banff Diagnostic Category 3: Suspicious (Borderline) For Acute T cell-Mediated Rjection (TCMR) and Category 4 TCMR**

Categories 3 and 4 can be considered as a continuum of increasingly severe manifestations of TCMR in the cortical tubulointerstitial compartment (borderline and acute TCMR IA, IB) and in the arterial compartment (acute TCMR IIA,

IIB, III, chronic-active TCMR II). Frequently, Category 2 diagnoses of AMR also include Category 3 or Category 4 diagnoses as mixed AMR plus TCMR.

## **5 Banff Diagnostic Category 6: Other changes not considered to be caused by acute or chronic rejection**

The 8 officially recognised subcategories in 6 should be considered as examples rather than an exhaustive list. A number of other kidney transplant diseases can mimic rejection histologically, such as adenovirus nephropathy. To accurately and reliably diagnose these subcategories and other diseases and other *de novo* or recurrent nephropathies, a full triple diagnostic work-up as for native kidney biopsies is required. This includes standard paraffin histology with haematoxylin-eosin, periodic acid-Schiff, silver and trichrome stains, immunostaining for immunoglobulin heavy and light chains and complement factor 1 and 3 split products (usually C1q and C3c). This must be left to experienced nephropathologists.

## **6 Molecular diagnostics**

Molecular diagnostics, specifically RNA expression studies have been part of the Banff Classification for several iterations. In the Banff 2022 update, they are listed under ADPs as “Biopsy-Based Transcript Diagnostics For AMR/MVI Above A Defined Threshold, *If Thoroughly Validated For Use As A Substitute For AMR/MVI And Available*”. They have been used as evidence of antibody interaction with transplant tissue and as a surrogate parameter for the presence of donor-specific antibodies and even for a microscopy-based diagnosis of AMR. However, no assay has yet been officially recognised by the Banff Foundation as “thoroughly validated”. Frankly, it is not clear why the well-established [5, 6] commercial hybridisation assay is not considered “validated ... and available”, given the certainly inferior evidence for some other diagnostic criteria for AMR. Meanwhile, the Banff Foundation appears to have started the development cycle all over again on a different assay platform. This means that, although early results look promising [7, 8], the transplant community will have to wait for an officially recognised histomolecular platform.

## 7 Practical considerations and outlook

Routine diagnostics of renal transplant biopsies should be evidence-based, clinically relevant, economically feasible and follow international standards which are set by the Banff Classification. Centres should strive to achieve these goals as a multidisciplinary effort to the best of their ability. Ideally, all involved clinics and diagnostic institutes in a given transplant centre should agree on an evidence-based consensus definition for their daily routine diagnostics, taking into account their centre's resources, their experiences and emerging evidence.

It is increasingly recognised that alloreactive processes may not fit into the diagnostic boxes of the Banff Classification, but may be better defined by mechanism (TCMR vs. AMR), activity and chronicity, very similar to the biopsy assessment in lupus nephritis. Such novel concepts, the advent of digital nephropathology, computer vision and machine learning, and transcriptomics could lead to more reproducible and accurate diagnoses and pave the way for prognostic and theranostic classifiers.

## References

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