CHAPTER 6
Rejection

CHAPTER 6.1 Diagnosis and treatment of acute and chronic cellular transplant rejection

Lars Pape[1], Nele Kanzelmeyer[2], Jan Ulrich Becker[3] & Jun Oh[4]

[1] Department of Paediatrics II, University Hospital of Essen, Essen, Germany
[2] Department of Paediatric Nephrology, Hepatology, Metabolic and Neurology Diseases, Hannover Medical School, Hannover, Germany
[3] Department of Pathology, University Hospital of Cologne, Cologne, Germany
[4] Department of Paediatric Nephrology and Hepatology, University Hospital Eppendorf, Hamburg, Germany

ORCIDs:
Lars Pape: https://orcid.org/0000-0002-3635-6418
Nele Kanzelmeyer: https://orcid.org/0000-0002-4865-4906
Jan Ulrich Becker: https://orcid.org/0000-0003-2929-8085
Jun Oh: https://orcid.org/0000-0003-1846-675X

1 Introduction

Acute rejection occurs in 10–30% of patients on current immunosuppressive regimens during the first post-transplant year with higher rates in adolescents than in younger children [1]. The incidence of acute rejection peaks in the first year post-transplant and then declines [2]. Accurate diagnosis is crucial, as the presence and severity of rejection have a significant impact on long-term graft outcomes. While experiencing one or even more episodes of acute rejection does not necessarily reduce 5-year graft survival, it is associated with a greater decline in graft function (eGFR) [1].

2 Definition

Acute rejection is usually defined by the identification of specific histopathological changes in a renal biopsy [3], making the biopsy a key diagnostic tool. However, also clinical parameters, mostly referred to as Additional Diagnostic Parameters (ADPs) must also be considered (https://banfffoundation.org/

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central-repository-for-banff-classification-resources-3/; last accessed December 2024). The clinical presentation is often non-specific (e.g., swelling of the kidney on ultrasound, reduced urine output, possible weight gain; rarely fever, 'transplant pain', and increased blood pressure) or entirely absent. Therefore, the presumptive diagnosis is usually based on an elevated serum creatinine level. The presence or increase of albuminuria or haematuria may also indicate rejection or a recurrence of the underlying disease. Subclinical rejection may be detected in protocol biopsies [4], without any decrease of graft function.

3 Laboratory diagnostics

Blood tests: Creatinine (a 20% increase suggests rejection), urea, and donor-specific HLA antibodies (DD antibody-mediated rejection). If infection is suspected or to exclude it (depending on clinical focus): differential blood count, CRP, blood cultures, virology (CMV, BK polyomavirus), microbiology, and fungal testing.

Urine tests: U-protein/U-creatinine ratio, U-albumin/U-creatinine ratio, erythrocytes (for haematuria), leukocytes (to differentiate from urinary tract infection), urine culture (to differentiate from urinary tract infection).

4 Doppler ultrasound

Ultrasound should be performed routinely when acute rejection is suspected [5]. Key diagnostic issues include assessment of the size and echogenicity of the graft (swelling may indicate rejection, differential diagnosis [DD] could be pyelonephritis), detection of any urinary tract obstruction and measurement of vascular flow (DD arterial or venous thrombosis). Resistance indices (RIs) should be measured by ultrasound in at least two segmental arteries (an RI > 80% suggests rejection but with a low positive and negative predictive value).

5 Renal Biopsy

If acute rejection is suspected, a renal biopsy should always be performed within 24 hours (even at weekends). Histopathological examination of the light microscopic specimen should yield results within 8 hours (at least within 24 hours). The biopsy core should contain cortical, and medullary tissue to diagnose polyomavirus infection. At least one core should be obtained. The specimen should be transported in PBS-buffered 4% formalin, or if immunofluorescence is required, in Michel's fixative or fresh tissue, after consultation with the affiliated pathologist. The biopsy is graded according to the Banff Working Classification of Renal Allograft Pathology [3, Table 1], an international consensus revised every two years that provides criteria for diagnosis and biopsy quality. For example, a diagnostically valid renal biopsy requires the presence of at least 10 glomeruli and 2 arteries (or 7 glomeruli and 1 artery for a minimal sample).

Light and Electron Microscopy Diagnostics

Staining: Hematoxylin and eosin (HE), periodic acid-Schiff (PAS), and Jones silver, elastica staining.

Immunohistochemistry: C4d (as a diagnostic criterion for AMR), SV40 (to differentiate polyomavirus nephropathy), immunoglobulins and complement split products (routinely assessed one year post-transplant, to differentiate between relapse of the underlying disease or *de novo* glomerulonephritis).

If available, electron microscopy may be used to differentiate between relapse of the underlying disease, *de novo* graft glomerulonephritis, transplant glomerulopathy, or transplant peritubular capillaropathy. Diagnosis follows the Banff Classification (for the latest iteration see https://banfffoundation.org/central-repository-for-banff-classification-resources-3/; last accessed December 2024.

6 Treatment

Suspicious (borderline) for acute TCMR (Banff category 3)

Biopsy for cause: Give 4–6 intravenous boluses of (methyl)prednisolone at 300 mg/m^2 over 4–6 days (or methylprednisolone pulse therapy over 4 days (400 – 200 – 200 – 100 mg/m^2 body surface area per day as a short intravenous infusion over 15 minutes), followed by 1 mg/kg per day of intravenous

furosemide if needed. At the end of the course, the dose of oral (methyl)prednisolone may be increased and then gradually tapered. A possible treatment regime is as follows:

Week 1: 16 mg methylprednisolone/m^2 per day;
Week 2: 12 mg methylprednisolone/m^2 per day;
Week 3: 8 mg methylprednisolone/m^2 per day;
from week 4: 3 mg/m^2 per day, usually no more than 5 mg methylprednisolone

In the case of steroid-free immunosuppression, consider reintroduction of oral steroid therapy.

Monitor trough levels of CNIs (and/or everolimus) and MPA-AUC and increase CNI and antimetabolites if trough levels and/or MPA-AUC values are below target.

Protocol biopsy: The therapeutic relevance still remains unclear. In many cases, an unnecessary increase in immunosuppression can be avoided.

T-cell mediated rejection (Banff category 4)

≥ Banff IA: Administer 4–6 intravenous boluses of (methyl)prednisolone at 300 mg/m^2 over 4–6 days (or methylprednisolone pulse therapy over 4 days (400 – 200 – 200 – 100 mg/m^2 body surface area per day as a short intravenous infusion over 15 minutes), followed by 1 mg/kg per day of intravenous furosemide as needed. At the end of the course, the dose of oral (methyl)prednisolone may be increased and then gradually tapered. A possible treatment regime is as follows:

Week 1: 16 mg methylprednisolone/m^2 per day;
Week 2: 12 mg methylprednisolone/m^2 per day;
Week 3: 8 mg methylprednisolone/m^2 per day;
from week 4: 3 mg/m^2 per day, usually

In the case of steroid-free immunosuppression, consider reintroduction of oral steroid therapy.

1. If trough levels of maintenance immunosuppressants (measured 12 hours after oral administration) are low, adjust the trough levels based on the time since transplantation:

Cyclosporin A target trough levels after rejection:
- < 12 months post-transplant: 200–250 µg/L
- ≥ 12 months post-transplant: 150–200 µg/L

Tacrolimus target trough levels:
- < 12 months post-transplant: 15 µg/L
- 12 months post-transplant: 10 µg/L
- Determine the MPA-AUC and increase the MMF dose if necessary (see Chapter 4.2 and 4.3).

2. If on cyclosporin A-based immunosuppression, switch to tacrolimus:
   - Start tacrolimus therapy 12 hours after the last dose of cyclosporin A. Refer to the target trough levels mentioned above.
   - Increase the dose of MMF to achieve an MPA-AUC of ≥ 60 mg x h/L.
3. In patients receiving concomitant mTOR inhibitors, increase the dose as needed:
   - Target trough levels: everolimus, 6–7 µg/L; sirolimus, 8–10 µg/L

In cases of steroid resistance, defined as no or insufficient reduction in serum creatinine levels by the 4th to 6th day after initiation of methylprednisolone therapy (creatinine remaining at 150% or more of the baseline value), repeat transplant biopsy should be performed and, in most cases, therapy with anti-thymocyte globulin (ATG) should be initiated: start with 1.5 mg/kg/d over 3–5 days; dose adoption according to lymphocyte count, a cumulative dose of 8 mg/kg should be the maximum [6].

There are no protocols for the treatment of chronic active T cell-mediated rejection in children. Therapy may be initiated with steroid pulses followed by an increase of the maintenance immunosuppressive therapy.

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Table 1 BANFF 2022 diagnostic groups for diagnosis of acute rejection [3]

Category 1: Normal Biopsy or Nonspecific Change
Category 2: Antibody-mediated rejection and microvascular inflammation/injury (AMR/MVI)
- Active AMR
- Chronic active AMR
- Chronic 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);

Category 3: Suspicious (Borderline) For Acute TCMR
Category 4: TCMR
- *Acute TCMR IA* Banff Lesion Score i ≥ 2 AND Banff Lesion Score t2
- *Acute TCMR IB* Banff Lesion Score i ≥ 2 AND Banff Lesion Score t3
- *Acute TCMR IIA* Banff Lesion Score v1 regardless of Banff Lesion Scores i or t
- *Acute TCMR IIB* Banff Lesion Score v2 regardless of Banff Lesion Scores i or t
- *Acute TCMR III* Banff Lesion Score v3 regardless of Banff Lesion Scores i or t
- *Chronic Active TCMR Grade IA* Banff Lesion Score ti ≥ 2 AND Banff Lesion Score i-IFTA ≥ 2, other known causes of i-IFTA (eg, pyelonephritis, BK-virus nephritis etc.) ruled out AND Banff Lesion Score t2
- *Chronic Active TCMR Grade IB* Banff Lesion Score ti ≥ 2 AND Banff Lesion Score i-IFTA ≥ 2, other known causes of i-IFTA ruled out AND Banff Lesion Score t3
- *Chronic Active TCMR Grade II* Arterial intimal fibrosis with mononuclear cell inflammation in fibrosis and formation of neointima

Category 5: IFTA (Interstitial Fibrosis and Tubular Atrophy)
- *Mild*
- *Moderate*
- *Severe*

Category 6: Other Changes Not Considered To Be Caused By Acute Or Chronic Rejection

Polyomavirus Nephropathy, Posttransplant Lymphoproliferative Disorder, Calcineurin Inhibitor Toxicity, Acute Tubular Injury, Recurrent Disease, De Novo Glomerulopathy (Other Than TG), Pyelonephritis, Drug-Induced Interstitial Nephritis