

**Maine Medical Center
Maine Transplant Program
Policies and Procedures
Rejection Protocol**

Purpose

To define the parameters by which allograft rejection may be identified and managed.

Policy

It is the policy of the Maine Transplant Program (MTP) to identify and treat episodes of allograft rejection promptly in order to optimize outcomes.

Rejection Diagnosis

A diagnosis of rejection may be suggested by a change in allograft function, proteinuria or a rise in donor specific antibody.

The diagnosis of rejection is confirmed histologically.

Procedure

Kidney Transplant Biopsies

Kidney biopsies are performed by the renal fellow and are supervised by the transplant physician. Such tissue obtained is routinely processed for:

- Light microscopy (MMC)
- C4d (to BWH)
- BK virus Immunostaining (BWH)
- Immunofluorescence and electron microscopy are generally performed only if a recurrent or de novo glomerulopathy is suspected.

Allograft biopsies are read by an experienced nephropathologist and are reviewed contemporaneously and during pathology conference.

Allograft Pathology Classification

Kidney biopsy material is interpreted according to the Banff Diagnostic categories for renal allograft biopsies as follows:

1. Normal
2. Antibody mediated rejection
 - Acute AMR (C4d+) Type
 - I. ATN-like
 - II. Capillary-margination and or thrombosis
 - III. Arterial
 - Chronic active antibody mediated rejection
 - Glomerular double contours, peritubular capillary basement membrane multilayering, interstitial fibrosis, tubular atrophy, fibrous intimal thickening
3. Borderline changes
4. T-cell mediated rejection
 - Acute
 - IA. Significant interstitial infiltration (>25% of parenchyma) and moderate tubulitis
 - IB. Significant interstitial infiltration (>25% of parenchyma) and severe tubulitis
 - IIA. Mild to moderate intimal arteritis
 - IIB. Cases with severe intimal arteritis comprising > 25% of the luminal area
 - III. Transmural arteritis

Chronic active T cell mediated rejection

5. Interstitial fibrosis and tubular atrophy, no evidence of any specific etiology

Grade

- I. Mild (<25% of cortex)
- II. Moderate (26-50% of cortex)
- III. Severe (>50% of cortex)

6. Other: Categories not considered to be due to rejection. May coincide with categories 2-5.

Principles of Rejection Management

The nature of rejection dictates the intensity of rescue immunotherapy

The cause of rejection needs be identified

- Inadequate immunosuppression (under dosing, PK drug interactions)
- Non adherence to protocol which may be triggered any of the following issues:
 - Financial
 - Educational
 - Psychiatric disorder
 - Other
- Intercurrent events such as infection

Once parenteral rescue immunotherapy has been completed, patients will resume the oral steroid taper as follows:

- Pred 30mg daily x 14d
- Pred 25mg daily x 14d
- Pred 20mg daily x 14d
- Pred 15mg daily x 14d
- Pred 10mg daily x 14d
- Pred 5mg daily to continue indefinitely

Rescue Immunotherapy

T cell Mediated Rejection

Mild (Banff 1a)

Proposed outpatient steroid taper orally as follows

- Pred 100mg daily x 3d
- Pred 80mg daily x 3d
- Pred 60mg daily x 3d
- Pred 40mg daily x 3d
- Pred 20mg daily x 3d
- Pred 10mg daily with taper to 5mg/d within 1 month

- Optimize antimetabolite dosing
- Optimize CI levels
- Consider switch to Tacrolimus

Moderate Rejection (Banff 1b and above)

- Pulse methylprednisolone cumulative dose 1.5 to 3gm dose to be decided based on intensity and chronicity of rejection
- Switch to Tacrolimus
- Thymoglobulin if unresponsive or patient is beyond 1 year post transplantation

Vascular Rejection

- Switch to Tacrolimus
- Methylprednisolone 500mg IV as single dose then
- Thymoglobulin 1.5mg/kg daily for up to 14 days with appropriate premedications

Antibody Mediated Rejection

Diagnostic Criteria (need 3/4 to make Dx of AMR)

- Allograft dysfunction/AKI
- New or rising Donor Reactive Antibody titer
- Allograft histology
 - I: ATN
 - II: Cellular rejection-peritubular capillaritis
 - III: Vascular rejection
- Positive C4d staining

Antibody Mediated Rejection Treatment

- Methylprednisolone 1gm daily x 3d followed by oral steroid taper above
- Plasmapheresis
 - 1 plasma volume
 - Frequency: Alternate Day
 - Replacement fluid: Albumin
 - Goal: 6 treatments
- IVIg (100mg/kg/day- generally rounded to 10g/d) following pheresis.
- Consider rATG for antibody mediated vascular rejection
- Consider splenectomy, rituximab or eculizumab for refractory AMR

Non adherence

Non or suboptimal adherence with immunosuppression is an underlying contributor to many cases of rejection, particularly beyond the first year following transplantation.

For patients with identified non adherence with immunosuppression, additional consultations with the following as deemed necessary:

- Transplant Pharmacy
- Financial Coordinator
- Social work
- Psychiatry

Antimicrobial Prophylaxis

Patients who receive rescue immunotherapy for rejection are deemed to be at increased risk of infectious complications.

Patients who receive parenteral rescue immunotherapy will receive appropriate prophylaxis as described in the MTP policy “Antimicrobial Therapy” as follows:

- 1 month of oral candida prophylaxis
- PJP prophylaxis will be dictated by the intensity of rejection rescue therapy and will vary from 6 to 12 months.
- Antiviral prophylaxis is generally avoided though patients at risk for CMV will be screened by PCR

Resources

See order sets for

- Allograft biopsy
- Rejection
 - Mild
 - Moderate
 - Severe
- Antibody Mediated

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