Antibody Mediated Rejection Treatment Protocol

1. Baseline Testing

- Renal function, kidney biopsy
- Donor specific antibody (DSA) testing
- CD19 and C20 subsets

2. AMR Treatment Protocol (Day 1-15, Day 1 = treatment start date)

I. Steroids:

- Pulse methylprednisolone 500 mg IV daily x 3 on Day 1,2,3 then prednisone taper as per standard protocol
- Example: Prednisone 100 mg x1 → 75 mg x1 → 60mg x1 → 50 mg x1 → 40 mg x1 → 30 mg x1 → 20 mg OD for 4 weeks then slow taper to 5 mg OD

II. PLEX and IVIG[1-3]:

- PLEX + IVIG daily x 3 on Day 1,2,3 then 3 treatments per week for a minimum of 8 sessions. Additional treatments may be indicated based on clinical indication
- PLEX: 1.5x volume exchange for 3 treatments, then 1x volume exchanges thereafter. When performing PLEX within 48 hours of kidney biopsy replace with FFP, otherwise replacement with 5% albumin
- IVIG infusion: dosed 100 mg/kg/dose IV given after each PLEX
- Pre-medicate IVIG infusion with diphenhydramine 25-50 mg IV and acetaminophen 650 mg PO prior to IVIG

III. Rituximab (1-2 doses)[4]:

- Rituximab 375 mg/m^2/dose IV given on Day 4 (could be given after PLEX and IVIG if there is adequate time and space)
- Pre-mediate Rituximab infusion with:

  i. Diphenhydramine 50 mg PO/IV prior to Rituximab and Q4hr thereafter
  ii. Acetaminophen 650 mg PO 30 min prior to Rituximab and Q4hr thereafter

- Wait for a minimum of 24 hrs (ideally 48 hrs) before resuming PLEX after dosing Rituximab
- Repeat CD19 and CD20 counts after last plex – if CD19/20 $\geq$ 5 cells/mm^2, consider giving a second dose of Rituximab

IV. Optimization of maintenance immunosuppression:

- Increase MMF or Myfortic to full dose (MMF 1g BID and Myfortic 720 mg BID)
- Up-shift CNI target one level up

V. Follow-up and Surveillance:

- Consider repeat kidney biopsy before 1-month post treatment based on clinical indication (i.e. inadequate treatment response, worsening renal function, re-assess mixed TCR and AMR); if patient has good clinical response, consider biopsy at 1 month or later
- Repeat DSA testing at Day 15 (after finishing 8 PLEX sessions), Day 28

Supplement 1: Diagnosis of AMR

- Refer to Banff 2013 Criteria for AMR diagnosis[5]
- A simplified schematic is provided in Table 1

*Note: C4d positivity is no longer required for AMR diagnosis as long as a significant degree of microvascular injury is present (g+ptc ≥ 2)

*AMR treatment may be initiated if clinical and histologic evidence for AMR is strong and DSA and/or non-HLA antibody testing result is pending

	Acute/Active AMR	Chronic/Active AMR
Histology:	1. Microvascular injury: (g or ptc) 2. Arteritis 3. Thrombotic microangiopathy 4. ATN-unknown cause	1. Transplant glomerulopathy (cg) 2. Peritubular basement membrane duplication 3. Arterial intimal fibrosis
Serology:	Donor-specific antibodies (HLA, AT1R-Ab, MICA)	
Interaction:	C4d Moderate microvascular inflammation (g+ptc >= 2) Endothelial cell gene transcripts	

Table 1. Simplified criteria for diagnosis of AMR, based on Banff 2013 classification[5].

References

1. Montgomery RA, Zachary AA, Racusen LC, et al. Plasmapheresis and intravenous immune globulin provides effective rescue therapy for refractory humoral rejection and allows kidneys to be successfully transplanted into cross-match-positive recipients. *Transplantation.* 2000;70(6): 887-895.
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3. Sautenet B, Blancho G, Büchler M, et al. One-year Results of the Effects of Rituximab on Acute Antibody-Mediated Rejection in Renal Transplantation: RITUX ERAH, a Multicenter Double-blind Randomized Placebo-controlled Trial. *Transplantation.* 2016;100(2): 391-399.
4. Puisset F, White-Koning M, Kamar N, et al. Population pharmacokinetics of rituximab with or without plasmapheresis in kidney patients with antibody-mediated disease. *Br J Clin Pharmacol.* 2013;76(5): 734-740.
5. Haas M, Sis B, Racusen LC, et al. Banff 2013 meeting report: inclusion of c4d-negative antibody-mediated rejection and antibody-associated arterial lesions. *Am J Transplant.* 2014;14(2): 272-283.