**APPENDIX VI**


# Antibody Mediated Rejection in Renal Transplantation

## Guideline document

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# Contents



## 1. INTRODUCTION

These guidelines are intended for the treatment of antibody mediated rejection (AMR) following incompatible transplant (ABO and HLA) but may also be applied to AMR diagnosed following compatible transplantation [*i.e.* those without pre-formed anti-HLA donor specific antibodies (DSA) but with *de novo* DSA following transplantation].

Antibody mediated rejection (AMR) is now widely recognised as a major cause of graft failure. Major advances have been made in the diagnosis both in terms of histology and the detection of circulating DSA. Nevertheless, the optimum treatment for acute and chronic AMR remains unclear. To date there are few published randomised control trials examining the therapies currently used for acute and chronic AMR. Furthermore, studies are hampered by small numbers, heterogeneity of disease and interventions. A recent systematic review on the treatment of AMR found only five randomised controlled trials. Four of these were carried out before Banff formalised histological classification [1].

There are a number of on-going randomised control trials that may provide more reliable guidance on optimum treatment. This protocol has been generated on the basis of current evidence and recent guidelines published by The British Transplant Society [2].

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## 2. DIAGNOSIS OF AMR

### 2.1 Criteria for diagnosis

**Summary points**

- **C4d, DSA and histological evidence of microcirculatory injury all correlate with AMR and with each other but frequently all will not be present at diagnosis.**
- **C4d alone is NOT diagnostic (especially in ABOi transplantation).**
- **C4d negative AMR is well recognized (& included in latest Banff classification).**
- **Focal C4d staining in PTC may be significant if present with other factors (DSA, histology). It likely portends a worse allograft survival compared to absence of C4d deposition.**
- **AMR may be DSA negative (e.g. non-HLA antibody may be responsible).**

BTS guidelines recommend that the diagnosis of AMR can only be made following allograft biopsy. Therefore all patients with suspected AMR should undergo biopsy to confirm the diagnosis unless clinicians feel it is unsafe to do so (1C).
A patient should be screened for circulating DSA if they have histologically proven AMR on biopsy (1C).
There are a range of features (clinical, serological and pathological) to be considered in both diagnosis and management of AMR. These include major features:

- DSA
- C4d positivity in peritubular capillaries on biopsy
- Presence of microcirculatory inflammation (peritubular capillaritis/glomerulitis)
- Arteritis
- Presence of transplant glomerulopathy (indicates chronic AMR)

Other features which may indicate AMR:

- Acute tubular injury/acute tubular necrosis (ATN)
- Thrombotic microangiopathy (TMA)

Also severe T-cell mediated rejection (TCMR) may present at the same time as AMR (mixed rejection).

**2.2 Banff Criteria**

**Acute active AMR (*all three features must be present for diagnosis*):**

1. Histological evidence of acute tissue injury, including one of following:
    - Microcirculation inflammation (ptc >0 and/or g>0)
    - Intimal or transmural arteritis (v>0)
    - Acute thrombotic microangiopathy (in the absence of any other cause)
    - Acute tubular injury (in the absence of any other cause)

2. Evidence of current/recent antibody interaction with vascular endothelium, including at least one of the following:
    - Linear C4d staining in peritubular capillaries (ptc)
    - At least moderate microcirculation inflammation (g+ptc) ≥2

3. Serological evidence of DSA (in the absence of serological evidence despite histological features, a diagnosis of 'suspicious for AMR' is made) [3].

**Chronic active AMR (*all three features must be present for diagnosis*):**

1. Morphologic evidence of chronic tissue injury, including one or more of the following:
    - Transplant glomerulopathy (cg>0), if no evidence of TMA
    - Severe peritubular capillary basement membrane multilayering on EM
    - Arterial intimal fibrosis of new onset excluding other causes
2. Evidence of current/recent antibody interaction with vascular endothelium, including at least one of the following:
    - Linear C4d staining in ptc
    - At least moderate microcirculation inflammation (g+ptc) ≥2
3. Serological evidence of donor specific antibodies (DSA) HLA or other [3]

**C4d staining without evidence of rejection (*all three features must be present for diagnosis*):**

1. Linear C4d staining in peritubular capillaries
2. G=0, ptc=0, v=0, no TMA, no pertitubular capillary basement membrane multilayering, no ATI
3. No acute TCMR or borderline changes according to Banff criteria [3]

### 2.3 Caveats

**Isolated glomerulitis (*all three features must be present for diagnosis*):**

1. g>0 ptc=0, v=0, no TMA, no peritubular capillary basement membrane multilayering, no ATI
2. C4d staining negative
3. No acute TCMR or borderline changes according to Banff criteria [3]

**Intimal arteritis**

Intimal arteritis (v1 and v2) may be included in the lesions satisfying histologic criteria for AMR. In AMR it is associated with a worse prognosis. However, lesions are more commonly associated with mixed AMR/TCMR than with "pure" AMR and may be seen in pure TCMR in the absence of DSA. Intimal arteritis may be the only histologic manifestation of AMR ('isolated v lesions'), although this is uncommon [3].

## 3. TREATMENT

### 3.1 National guidelines

Given the lack of randomised control trials, the optimal treatment for AMR is uncertain. KDIGO guidelines suggest AMR should be treated with one or more of the following (with or without steroids); plasma exchange, intravenous immunoglobulin (IVIg), anti-CD20 antibody and lymphocyte-depleting antibody (level 2C or less) [4].
For patients who have an antibody incompatible transplant recipients with acute AMR, BTS guidelines are as follows:

<u>Recommend</u>

- Patients receive or are switched to baseline maintenance treatment with tacrolimus, mycophenolate mofetil and steroids at usual maintenance doses and treated with high dose steroids (1C).
- Patients receive extracorporeal antibody removal with five cycles of treatment or until the DSA is no longer detectable (1C).

<u>Suggest</u>

- IVIg, rituximab or bortezomib may be used in combination with other agents unless evidence emerges to the contrary (2D)
- Eculizumab may be considered for rescue therapy in resistant acute AMR in cases which are C4d positive or the DSA have complement fixing properties (2D)
- Splenectomy (with or without eculizumab) may be considered to rescue AMR presenting with acute onset oliguria/anuria in the early period after antibody incompatible transplant (2D) [1]

### 3.2 Summary of therapeutic options and management

Where a positive diagnosis of AMR is made the patients should receive IV pulsed methylprednisolone (500 mg x3).
Additional immunosuppression will be determined by other clinical features (see table below)

| Category | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| **DSA** | + | - | + | - | - | + |
| **C4d** | +/- | +/- | +/- | +/- | + | - |
| **Microcirculatory inflammation** | + | - | + | + | - | - |
| **Arteritis** | + | + | - | - | - | - |
| **Treatment** | **PEX, IVIg, ATG** | **Consider ATG** | **PEX, IVIg, Consider Bortezomib *** | **Consider treatment as for category 3 Early re-biopsy †** | **Monitor, Early re-biopsy** | **Monitor, re-biopsy depending on renal function or DSA rise** |

DSA: Donor specific antibodies, PEX: Plasma exchange; IVIg: Intravenous immunoglobulin; ATG: Anti-thymocyte globulin

* **Decision to give Bortezomib must be discussed with MDT.**
Decision may depend on the level of DSA. Current advice is to consider Bortezomib if DSA >4000 MFI or > 2000 MFI after 3 months in the presence of histological features of AMR.

† **Look for other features of AMR including ATN and/or TMA-if present consider treatment**
If microcirculation inflammation is limited to isolated glomerulitis, then current evidence does not support intervention but would advise early re-biopsy

### 3.3 Suggested therapies and rationale

**Treatment of Acute active AMR**

Early diagnosis is key to preserving function and good outcomes can be expected with treatment of early acute AMR. Suggested initial treatment includes:

**IV Methylprednisolone** at dose of 500mg for 3 days.

**Plasmapheresis**: Minimum of 5 sessions of full plasma volume exchanges on alternate days [5, 6]. Further exchanges will depend on initial MFI of DSA and response to treatment

**IVIg (Octagam)**: 100mg/kg after each exchange. Consider higher dose at the end of the final exchange to give a cumulative dose of at least 1g/kg [5, 6].

Check DSA after last plasmapheresis: send sample **before** IVIg is administered or else several days later, as it may lead to false positive results.

**Severe or Refractory Cases**
Additional treatment may be warranted in high-risk cases, cases with severe histological injury or cases refractory to the above treatment.

**Bortezomib:** If cumulative MFI is persistently high (i.e. MFI >4000 early or >2000 at three months) then consider Bortezomib for a maximum of two cycles. A cycle consists of 4 injections of Bortezomib 1.3mg/$m^2$ subcutaneously administered over two weeks-generally day 1, 4, 8, 11.

**Anti-thymocyte globulin (ATG)**: If evidence of intimal or transmural arteritis with or without other features of acute TCMR, consider adding ATG to plasmapheresis and IVIg (see main protocol for dosing information).

- If ATG is to be added to AMR treatment, for severe TCMR (≥Banff IIA) or adjuvant therapy for AMR, this can provide logistical challenges as it may be desirable to give plasmapheresis, IVIg & ATG.

- In this instance, ATG may be administered post plasmapheresis. IVIg may be given as 2 doses of 500mg/kg (i.e. cumulative 1g/kg) after plasmapheresis/ATG is complete.

- Note that ATG may also have some anti-B cells effects and therefore may be beneficial in resistant AMR.

**Eculizumab**: If evidence of acute thrombotic microangiopathy (in the absence of any other cause), there may be a rationale for seeking approval to use anti-C5a inhibitor. This is usually reserved as salvage therapy for cases of severe AMR with evidence of endothelial injury as a result of antibody interaction with the vascular endothelium.

**Mixed (AMR and TCMR) rejection**
Simultaneous occurrence of AMR and TCMR or "mixed rejection" is common especially in late presentations with non-adherence/under-immunosuppression. It frequently has a predominance of Class II DSA, established chronic histological features and a bad prognosis. ATG may be a therapeutic option (see above).

**Treatment of chronic active AMR**
Late (>6 months) AMR is less responsive to any current therapeutic intervention and is likely to progress to transplant glomerulopathy and ultimately allograft failure irrespective of treatment. Maintenance immunosuppression should be reviewed and if not already taking it, patient should be switched to MMF (greater anti-B cell effect compared to azathioprine), tacrolimus and steroids increased or re-introduced.
Any of the above interventions may be considered in addition to the above if consensus is that histology demonstrates microcirculation inflammation and chronic scarring is minimal.

In practice, therapeutic interventions rarely extend beyond methyl prednisolone, plasmapheresis and IVIg. Bortezomib may be considered if the patient has persistent DSA but the evidence base for use in chronic active AMR is currently lacking [17].

**Chronic AMR/transplant glomerulopathy**

Chronic AMR is much less likely to respond to treatment so the degree of IF/TA and transplant glomerulopathy should be assessed before a decision to treat is made.

There is no clear benefit with any intervention for late AMR, including with novel therapies (rituximab/bortezomib) [17]. Consider maximizing immunosuppression & switching to tacrolimus/MMF if not already these agents.

If treatment is considered in chronic AMR, there should be evidence of at least some ongoing activity.

If treatment is considered in chronic AMR, the full protocol may be individualized e.g. plasmapheresis is likely of no benefit in this setting and may be omitted.

## Appendix: Evidence base

Caveats:

i. Most evidence is in the form of case series and uncontrolled studies, often using historical cohorts as comparators, and usually only reporting positive outcomes leading to possibility of reporting bias.

ii. The exact diagnosis in many studies is imprecise. Like real life, many have either DSA or C4d+ but not both and histological lesions reported are often incomplete.

Rituximab:

Rituximab has one RCT showing no benefit [7] and many uncontrolled studies/case series showing benefit [8], including the addition of rituximab AND plasmapheresis to IVIg which showed benefit versus IVIg alone in an historical cohort [9]. This makes it impossible to ascertain which of rituximab or plasmapheresis (or both or none) led to the improvement. The largest retrospective study of 54 patients included half receiving rituximab 500mg once-off with both groups receiving plasmapheresis [10]. IVIg was only given if IgG was low (n=2) and benefit was seen in the rituximab group. However, another historical cohort showed much less impressive results with rituximab (see comparison with bortezomib below) [11].

Bortezomib:

Bortezomib is accumulating non-randomized and uncontrolled studies suggesting benefit [8-10], including versus an historical small rituximab cohort [11]. In this study, patients received either one cycle of bortezomib or a fixed dose 500mg of rituximab (historical cohort). At 18 months, graft survival was 6/10 in the bortezomib group as compared to 1/9 in the rituximab group. Moreover, serum creatinine at 9 months was 2.5 ± 0.6 (bortezomib) versus 5.1 ± 2.1 mg/dL

(rituximab). In the series by Flechner *et al* (n=20), one cycle (=4 doses) was administered along with steroids and IVIg at mean of 20 months post-transplant. Graft survival was 85% at 10 months and benefit was mostly in those with creatinine <3g/dL and low level proteinuria [13]. Its anti-plasma cell mechanism seems like an attractive target but randomized trials are lacking at present.
Most series have used one cycle (4 doses of subcutaneous 1.3 mg/$m^2$ days 1, 4, 8, 11) extrapolated from the myeloma literature. The utility of additional cycles is unclear at this point but may be considered if ongoing evidence of AMR is present, with some evidence of benefit from the initial cycle (drop in DSA, improvement in histological feature, renal function etc.).

Eculizumab:
Eculizumab has a few case reports as salvage treatment, suggesting benefit [15], and some reporting no benefit [16] (at least in C4d negative AMR), but no robust data. It is precluded in routine management due to cost.

References:


1. Roberts DM, Jiang SH, Chadban SJ. The treatment of acute antibody-mediated rejection in kidney transplant recipients - a systematic review. Transplantation 2012; 94: 775-83.
2. BTS guidelines, 2016
3. 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: 272-83
4. KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant 2009; 9 (Supplement 3).
5. R A Montgomery, A A Zachary, LC Racusen 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, vol. 70, no. 6, pp. 887–895, 2000.
6. Rocha PN, Butterly DW, Greenberg A, Reddan DN, Tuttle-Newhall J, Collins BH, Kuo PC, Reinsmoen N, Fields T, Howell DN, Smith SR. Beneficial effect of plasmapheresis and intravenous immunoglobulin on renal allograft survival of patients with acute humoral rejection. Transplantation. 2003 May 15;75(9):1490-5.
7. Sautenet B, Blancho G, Buchler M, et al. One year results of the effects of rituximab on acute humoral rejection in renal transplantation: RITUX ERAH, a multicenter randomized placebo controlled trial. Am J Transplant 2013; 13 (Suppl 5, Abstract #266): 112.
8. Mulley WR, Hudson FJ, Tait BD, Skene AM, Dowling JP, Kerr PG, Kanellis J. A single low-fixed dose of rituximab to salvage renal transplants from refractory antibody-mediated rejection. Transplantation. 2009;87(2):286.
9. Lefaucheur C, Nochy D, Andrade J, et al. Comparison of combination plasmapheresis/IVIg/anti-CD20 versus high dose IVIg in the treatment of antibody-mediated rejection. Am J Transplant 2009; 9: 1099.
10. Kaposztas Z, Podder H, Mauiyyedi S, et al. Impact of rituximab therapy for treatment of acute humoral rejection. Clin Transplant 2009; 23: 63.
11. Waiser J, Budde K, Schütz M, Liefeldt L, Rudolph B, Schönemann C, Neumayer HH, Lachmann N. Comparison between bortezomib and rituximab in the treatment of antibody-mediated renal allograft rejection. Nephrol Dial Transplant. 2012 Mar;27(3):1246-51.
12. Everly MJ, Everly JJ, Susskind B, Brailey P, Arend LJ, Alloway RR, Roy-Chaudhury P, Govil A, Mogilishetty G, Rike AH, Cardi M, Wadih G, Tevar A, Woodle ES. Bortezomib provides effective therapy for antibody- and cell-mediated acute rejection. Transplantation. 2008 Dec 27;86(12):1754-61.
13. Flechner SM, Fatica R, Askar M, Stephany BR, Poggio E, Koo A, Banning S, Chiesa-Vottero A, Srinivas T. The role of proteasome inhibition with bortezomib in the treatment of antibody-mediated rejection after kidney-only or kidney-combined organ transplantation. Transplantation. 2010 Dec;90(12):1486-92.
14. Everly MJ. An update on antibody reduction and rejection reversal following bortezomib use: a report of 52 cases across 10 centers. Clin Transpl. 2010:353-62.
15. Locke JE, Magro CM, Singer AL, Segev DL, Haas M, Hillel AT, King KE, Kraus E, Lees LM, Melancon JK, Stewart ZA, Warren DS, Zachary AA, Montgomery RA. The use of antibody to complement protein C5 for salvage treatment of severe antibody-mediated rejection. Am J Transplant. 2009;9(1):231.
16. Burbach M, Suberbielle C, Brochériou I, Ridel C, Mesnard L, Dahan K, Rondeau E, Hertig A. Report of the inefficacy of eculizumab in two cases of severe antibody-mediated rejection of renal grafts. Transplantation. 2014 Nov 27;98(10):1056-9
17. Gupta G, Abu Jawdeh BG, Racusen LC, Bhasin B, Arend LJ, Trollinger B, Kraus E, Rabb H, Zachary AA, Montgomery RA, Alachkar N. Late antibody-mediated rejection in renal allografts: outcome after conventional and novel therapies. Transplantation. 2014 Jun 27;97(12):1240-6.