1. Introduction

Transplantation offers better survival and quality of life to those able to undergo the procedure. The widespread use of potent and specific immunosuppressive agents has significantly reduced acute rejection rates but the diagnosis and treatment of Antibody Mediated Rejection (ABMR) remains challenging with two different clinical phenotypes identified: clinical phenotype 1 occurs early post- transplant and is associated with preformed Donor Specific Antibodies (DSA) while clinical phenotype 2 is related to formation of de novo DSA later in the life of the transplant; both present acute inflammation, cell damage and lysis of endothelial cells. Subclinical rejection is present when there are acute histologic changes but no abnormalities in creatinine and GFR. Chronic ABMR represents a form of rejection in which there is no acute inflammation and there is evidence of chronic tissue damage, with abnormal creatinine and proteinuria.

The Banff classification for ABMR has 3 categories: 1) Active ABMR; 2) Chronic active ABMR; 3) Chronic ABMR. It is possible that patients can present ABMR at the same time as T-cell mediated rejection (TCMR).

Acute and chronic ABMR are associated with poor outcomes after kidney transplantation. Patients with *de novo* DSA tend to have a worse prognosis compared to patients with pre-existing DSA (34% vs 63% graft survival at 8 years). Specifically, patients with acute ABMR are at greater risk for subsequent rejection, transformation into chronic ABMR and graft loss. Therefore, early diagnosis and evidence based treatment is essential in order to minimize graft loss and maximize long term graft and patient outcome.

2. Scope

Kidney and pancreas-kidney transplant.

3. Recommendations, Standards and Procedural Statements

This guideline covers most instances of acute ABMR (presumed and confirmed). With confirmed acute ABMR, the standard of care includes intravenous (IV) steroids, IV immunoglobulin (IVIg) and plasmapheresis (PLEX). Rituximab and other agents are not part of the standard of care and require individual consideration and MDT discussion including nephrology, transplant, renal pharmacist and transplant laboratory. Chronic-active ABMR and chronic ABMR are not covered by this guideline.

3.1 Diagnosis

Clinically, acute rejection is defined as an acute deterioration in graft function associated with specific pathologic changes seen on transplant biopsy. ABMR is caused by donor specific antibodies to Class I and Class II HLA antigens although other non-HLA antigens have also been recognized.

The Banff criteria for classifying acute humoral rejection require the presence of:

1. Histological evidence of acute tissue injury including: glomerulitis (g) and peritubular capilaritis (ptc); also can show endarteritis (v), acute tubular injury and acute thrombotic microangiopathy;
2. Evidence of antibody interaction with endothelium: C4d in peritubular capillaries; or microvascular inflammation (g + ptc); or increased expression of gene transcripts in the

biopsy strongly associated with ABMR

3. Serologic evidence of circulating DSA (but criteria 2 could substitute this) Complement system can be activated by the alternative and lectin pathways and hence C4d may not always be positive in ABMR. Testing for non-HLA antibodies can be considered too

Refer to the latest Banff classification for the complete updates and the rationale (Loupy 2020)

3.2 Treatment (see table below)

- Optimisation of baseline immunosuppression
  (increasing doses of mycophenolate and tacrolimus)
- Methylprednisolone (MPDN) intravenous 500 mg/day x 3 doses, followed by 30mg oral prednisolone (to follow a reduction dosing regimen, reduction regimen not specified but as per treating physician/surgeon preference)
- Plasma exchange (PLEX) for 7 sessions (course can vary based on individual characteristics). The exchange volume is calculated as 1.5 plasma volume with the following formula:

  $$PV = TBV \times (1 - Hct)$$

  PV: Plasma volume, TBV: Total blood volume, Hct: Haematocrit

  Exchange volume is provided with serum human albumin 5%; one to two units of fresh frozen plasma (FFP) may be used for replacement at the end of a plasmapheresis treatment to reduce bleeding risk in the appropriate clinical setting, such as a same-day kidney allograft biopsy
- Intravenous Immunoglobulin (IVIg) 2 doses of 1g/kg of ideal body weight adjusted dosing; IVIg has to be approved for use by the immunoglobulin panel and relevant form must be submitted prior to request supply from pharmacy. http://insitetogether.xuhl-tr.nhs.uk/SP2007/Medicines%20Information/Procedure%20for%20out%20of%20hours%20Ig.pdf

Treatment	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9-23	Day 23 onwards
MPDN	500 mg IV	500 mg IV	500 mg IV	Pred 30mg OD	Continue oral prednisolone – gradual dose reduction					
IVIg	-	-	1g/kg	-	-	-	-	1g/kg	-	-
Plasma exchange	PLEX #1	PLEX #2	PLEX #3	-	PLEX #4	PLEX #5	PLEX #6	PLEX #7	-	-
Rituximab	-	-	-	-	-	-	-	-	1g	1g

***IVIg is to be given after PLEX session 3 and 7**

****Rituximab intravenous 1g x 2 doses (given 2 weeks apart) – rituximab may not be used for all cases and decision to use will be by joint discussion between transplant surgeon and transplant nephrologist**

Special considerations:

Patients with ABMR should be counselled about complications of treatment, as increased risk of infections (including opportunistic diseases), allergic reactions, abnormalities in electrolytes/fluid volume, steroids side effects, etc.

Consider appropriate prophylaxis for CMV, fungal and pneumocystis infections.

Check for HIV, hepatitis B, C and Tb (IGRA test, such as QuantiFERON-TB) serology prior to administration of rituximab and obtain consent (follow safety checklist prior to prescribing on rituximab chart in appendix 1).

3.3 DSA Monitoring:

DSA monitoring is currently done by Luminex technology which is a solid phase assay, it was developed to be a qualitative assay and not a quantitative one and any interpretation of an antibody's Median Fluorescence Intensity (MFI) should reflect this. Please check with the Head of Transplant Laboratory before requesting DSA. Antibody runs are done twice per week (usually Tuesday and Thursday) and a serum sample should reach the lab latest before 10:00 in the morning. For urgent results please contact H&I lab on ext. 14607. Below is a guide to DSA monitoring for patients that develop acute ABMR:

1. DSA around the time of biopsy
2. After first round of PLEX (7 as per above protocol)
3. At the end of ABMR treatment to assess response
4. Subsequent DSA monitoring will be on an individual case by case basis

Refer to the Transplant Laboratory Service User Manual for further information about DSA testing.

3.4 Rationale:

3.4.1 Plasmapheresis

Plasmapheresis removes circulating DSA and is used in desensitisation protocols as well as in the treatment of ABMR. Different techniques used include plasma exchange and immunoadsorption, the latter now rarely used. Whilst historic observational studies had mixed conclusions on the benefit of plasmapheresis in the treatment of ABMR, one of the few RCTs in the treatment of ABMR had to be terminated due to the significant benefit seen in the interventional arm receiving immunoadsorption. Whilst there are recognised differences between immunoadsorption and plasma exchange, the principle of antibody removal is similar. This is shown from the published data, predominantly from desensitisation protocols on the effectiveness of rapid HLA antibody removal following plasma exchange.

3.4.2 Intravenous immunoglobulin

IVIg has numerous potential effector mechanisms which could attenuate the treatment of ABMR, these include the ability to neutralise circulating DSA, inhibition of complement activation, decreases in the production of proinflammatory cytokines and blocking immune activation by competing for FcγR. Intravenous immunoglobulin has been shown to reduce degree of allosensitisation in highly sensitised renal patients on the transplant wait list and is frequently used in protocols for the prevention or treatment of alloimmune injury. However, there is no significant evidence to show its efficacy for the indication of treating ABMR when used in isolation. Recommendations by the British Transplant Society, CQUIN and other international groups advocate for the use of IVIg in the treatment of AMBR.

3.4.3 Rituximab and bortezomib

Biological agents targeting B-cells, plasma cells and their derivatives have been increasingly used

as adjuvant therapy in both desensitisation and ABMR treatment protocols for nearly two decades but the evidence remains low at best. The antibodies rituximab and bortezomib have been the most frequently studied.

Rituximab is a B-cell depleting monoclonal antibody directed against CD-20. Following its administration, rituximab depletes both immature and mature B-cells but not plasma cells nor memory B cells. Early case reports and series suggested a benefit of the addition of rituximab to the standard treatment protocols of ABMR; *as such, rituximab is now the commonest add-on agent used in the treatment of acute ABMR*. The only randomised controlled trial, Ritux-ERAH, analysed the effectiveness of rituximab versus placebo in 38 patients with acute ABMR receiving plasmapheresis, IVIg and corticosteroids; these were patients with rejection in the first year of transplantation, with 57% presenting ABMR in the first month. At day 12 (primary endpoint) there was not difference in the absence of significant improvement in renal function and the changes in creatinine were similar in both groups; at one year, there was no benefit of adjuvant rituximab in terms of allograft survival; the study was underpowered and showed more opportunistic infections in the rituximab group. A second analysis of the trial, 7 years later, showed no difference in outcomes for patients who received rituximab versus those who received placebo, and although the rituximab group had higher number of opportunistic infections and cancers, there was not a significant difference.

Bortezomib has been studied in the BORTEJECT trial, which included patients with late rejection and standard immunosuppression. The study showed no benefit in using bortezomib and the treatment was associated with substantial toxicity.

3.5 Other considerations

It is important that other causes of kidney dysfunction are ruled out; they include: viral infections (CMV, BK virus), ascending infection (urinary tract infections and pyelonephritis), interstitial nephritis, post-transplant lymphoproliferative disease (PTLD) and poor perfusion/obstruction.

The primary use of other agents, such as tocilizumab, imlifidase, eculizumab, ATG, is discouraged. There are some circumstances in which they can be considered, but they need approval of the transplant MDT and it is also sensible to inform the Head of Service and managers, as those treatments might need approval from Medical Director or national bodies.

ABMR in the setting of ABO incompatible transplant presents a very rapid course and tends to be very aggressive and somehow more resistant to treatment compared to the standard ABMR. MDT discussion for treatment is encouraged.

There are instances in which patients can present both acute antibody mediated rejection (ABMR) and T-cell mediated rejection (TCMR). These patients are at very high risk of graft loss and their treatment should be discussed with the kidney transplant MDT. Usually they require both treatments for ABMR and TCMR (treatment can be given on alternate days, avoiding giving rATG-Thymoglobulin on the same day as PLEX to avoid clearance) and repeated biopsies to assess response.

5. Education and Training

This guideline formalises what is now current practise in the unit and as such there is no requirement for additional training but the guideline will be distributed to all renal and transplant staff members for awareness.

6. Monitoring and Audit Criteria

Key Performance Indicator	Method of Assessment	Frequency	Lead

Incidence of ABMR	Biopsy and information from Proton	Every 2 years	MDT
1 year creatinine post ABMR	Proton	Every 2 years	MDT
Opportunistic infections at 1 year post ABMR treatment	Proton	Every 2 years	MDT

7. Legal Liability Guideline Statement

See section 6.4 of the UHL Policy for Policies for details of the Trust Legal Liability statement for Guidance documents

8. Supporting Documents and Key References

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8. Key Words

Antibody mediated rejection, renal transplant, pancreas-kidney transplant, rituximab, immunoglobulin, transplant rejection.

APPENDIX 1

University Hospitals of Leicester Renal and Transplant Services

CONSULTANT

……

RITUXIMAB CHART 1g One or two doses

PRESCRIBING, ADMINISTRATION AND MONITORING

Drug Sensitivities

Date recorded	*Drug*	*Reaction*

Patient Name

Indication for Rituximab

Vasculitis	
ABOi transplant	
Other (please state)	

Pre-assessment Checklist

Date recorded	
Number of infusions planned	
Interval between infusions	
Immunoglobulins	
Lymphocyte subsets (if indicated)	
FBC, LFT review	
Hepatitis B Screen negative	
consider TB risk (CXR, Quantiferon)	
Pregnant or Breast feeding	
Current Infection	
Recent exposure to chickenpox or shingles	
Should not have had live Vaccination in last 4 weeks Check status of annual inactivated flu and 5 yearly pneumovax vaccine (ideally given at least 3 weeks before infusion).	
Discussed Co-trimoxazole prophylaxis	
Ask to withhold antihypertensive and analgesic medication on morning of infusion if appropriate.	
Information leaflet given	
Signature	

University Hospitals of Leicester Renal and Transplant Services

CONSULTANT

……

RITUXIMAB CHART
1g
One or two doses

Patient Name and S number or label

1st RITUXIMAB INFUSION

Date	Time	Premedication drugs	Route	Dose	Signature/ print name	Time Given	Given by/Checked by Signature/Print name	
		Paracetamol	oral	Please circle dose 500mg/1g				
		Chlorphenamine	iv	10mg				
		Hydrocortisone	iv	100mg				
		Methylprednisolone (if required)	iv					
Start giving Rituximab 60minutes after hydrocortisone or methylprednisolone infusion has finished. Use a new giving set. Prepare Rituximab as a 2mg/ml solution in sodium chloride 0.9%. **Patients will receive biosimilar Rituximab unless otherwise specified by the prescriber.**								
		RITUXIMAB in 500mls of sodium chloride 0.9%	iv	1g				

Preparation and Administration check list

1. Check that pre-assessment has been performed and signed by a consultant
2. Check the patient has not received analgesics containing paracetamol in the last 4 hours
3. check the patient has omitted their morning dose of any-antihypertensive medication
4. Take baseline temperature, pulse, BP and oxygen saturations
5. Insert peripheral cannula
6. Check infusion pump is ready and working
7. Administer pre-infusion medication 60 minutes before Rituximab is given
8. For 1g dose withdraw 100mls of sodium chloride 0.9% from a 500ml bag and discard
9. Add 100mls of Rituximab 10mg/ml to the contents in the bag to give a final volume of 500mls and final concentration of 2 mgs/ml
10. If first infusion was well tolerated then commence at 50ml/hour for 30minutes then increased by 25ml/hr every 30minutes
11. If patient shows any sign or symptom of a reaction slow the rate or stop the infusion. When symptoms improve continue the infusion at half the rate of infusion prior to the reaction

ADMINISTRATION OF FIRST RITUXIMAB INFUSION

Infusion started at……(time)…….(date)

Time from start of infusion	Infusion Rate (mL/hour)	Rate if patient reacts	Observations				Comments	Signature/Print name
			T	P	BP	O_2 Sats		
Baseline obs								
0-30mins (50mg/hour)	25							
31-60mins (100mg/hour)	50							
61-90mins (150mg/hour)	75							
91-120mins (200mg/hour)	100							
121-150mins (250mg/hour)	125							
151-180mins (300mg/hour)	150							
181-210mins (350mg/hour)	175							
211- end (400mg/hour)	200							

Infusion finished at……(time)… …(date)

University Hospitals of Leicester Renal and Transplant Services

CONSULTANT

……

RITUXIMAB CHART
1g
One or two doses

Patient Name and S number or label

2nd RITUXIMAB INFUSION

Date	Time	Premedication drugs	Route	Dose	Signature/ print name	Time Given	Given by/Checked by Signature/Print name	
		Paracetamol	oral	Please circle dose 500mg/1g				
		Chlorphenamine	iv	10mg				
		Hydrocortisone	iv	100mg				
		Methylprednisolone (if required)	iv					
Start giving Rituximab 60minutes after hydrocortisone or methylprednisolone infusion has finished. Use a new giving set. Prepare Rituximab as a 2mg/ml solution in sodium chloride 0.9%. **Patients will receive biosimilar Rituximab unless otherwise specified by the prescriber.**								
		RITUXIMAB in 500mls of sodium chloride 0.9%	iv	1g				

Preparation and Administration check list

1. Check that pre-assessment has been performed and signed by a consultant
2. Check the patient has not received analgesics containing paracetamol in the last 4 hours
3. check the patient has omitted their morning dose of any-antihypertensive medication
4. Take baseline temperature, pulse, BP and oxygen saturations
5. Insert peripheral cannula
6. Check infusion pump is ready and working
7. Administer pre-infusion medication 60 minutes before Rituximab is given
8. For 1g dose withdraw 100mls of sodium chloride 0.9% from a 500ml bag and discard
9. Add 100mls of Rituximab 10mg/ml to the contents in the bag to give a final volume of 500mls and final concentration of 2 mgs/ml
10. If first infusion was well tolerated then commence at 50ml/hour for 30minutes then increased by 25ml/hr every 30minutes
11. If patient shows any sign or symptom of a reaction slow the rate or stop the infusion. When symptoms improve continue the infusion at half the rate of infusion prior to the reaction

ADMINISTRATION OF SECOND RITUXIMAB INFUSION

Second infusion chart -If first infusion is well tolerated

Infusion started at……(time)…....(date)

Time from start of infusion	Infusion Rate (mL/hour)	Rate if patient reacts	Observations				Comments	Signature/Print name
			T	P	BP	O_2 Sats		
Baseline obs								
0-30mins (100mg/hour)	50							
31-60mins (150mg/hour)	75							
61-90mins (200mg/hour)	100							
91-120mins (250mg/hour)	125							
121-150mins (300mg/hour)	150							
151-180mins (350mg/hour)	175							
181-end (400mg/hour)	200							

Infusion finished at……(time)… ...(date)

As Required Medications:

Drug (approved name): **Paracetamol**

Route:	Dose/ Freq	Start Date	Sig:
po	500mg-1g 4-6hrly (max 4g in 24 hrs) For pain or pyrexia		

Date																
Time																
Dose																
Given/ 2nd Sig.																

Drug (approved name): **Chlorphenamine**

Route:	Dose/ Freq	Start Date	Sig:
IV			

Date																
Time																
Dose																
Given/ 2nd Sig.																

Drug (approved name): **Hydrocortisone**

Route:	Dose/ Freq	Start Date	Sig:
IV			

Date																
Time																
Dose																
Given/ 2nd Sig.																

Drug (approved name): **Salbutamol**

Route:	Dose/ Freq	Start Date	Sig:
neb			

Date																	
Time																	
Dose																	
Given/ 2nd Sig.																	

10mg 6hrly as required			

100-200mg			

2.5mg			

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This table is used to track the development and approval and dissemination of the document and any changes made on revised / reviewed versions

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REVIEW RECORD

Date	Issue Number	Reviewed By	Description Of Changes (If Any)
03/02/2020		MDT	Rituximab specific drug chart add and change to Truxima
November 2020		MDT	Added rituximab chart as Appendix 1 and updated IVIg and PLEX schedule
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