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 cellular rejection rates but the diagnosis and treatment of Antibody Mediated Rejection (AMR) remains challenging with two different clinical phenotypes identified, clinical phenotype 1 occurs early post-transplant and is associated with preformed Donor Specific Antibody's (DSA) while clinical phenotype 2 is related to denovo DSA and leads to chronic AMR (1).

More than 20,000 patients awaiting kidney transplantation in the United States are sensitised (typically owing to blood transfusion, pregnancy or previous transplants) to HLA class I and/or class II antibodies. A common approach to AMR prevention has been to avoid transplanting highly sensitised patients. However, avoiding transplant renders chronic dialysis the only option, with implications for patient survival, quality of life, as well as healthcare costs (1). Acute and chronic AMR are associated with poor outcomes after kidney transplantation. Specifically, patients with acute AMR are at greater risk for subsequent rejection, chronic AMR 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 kidney pancreas transplant.

3. Recommendations, Standards and Procedural Statements

This guideline will cover the criteria for diagnosis of clinical phenotype 1 acute AMR and its treatment. This guideline does not cover treatment of de novo Donor Specific Antibody (DSA) induced AMR occurring in the late post-transplant period, de novo AMR is a different clinical phenotype and although its treatment does mirror that of acute AMR, every component of acute AMR treatment may not be used in de novo DSA induced AMR as the treatment approach is case dependant.

3.1 Diagnosis

Clinically, acute rejection is defined as an acute deterioration in graft function associated with specific pathologic changes seen on transplant biopsy. Acute humoral rejection 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 (a) histological evidence of acute tissue injury e.g. acute tubular necrosis, capillaritis, tubulitis, arteritis, glomerulitis (b) presence of circulating DSA, and (c) immunologic evidence of an antibody-mediated process with positive peritubular capillary C4d staining reflecting complement activation via the classical pathway (2). We now know that the complement system can be activated by the alternative and lectin pathways and hence C4d may not always be positive in AMR (3).

Two out of three of the below criteria are required for diagnosis of AMR, this is taking in to consideration new entity of C4d –ve AMR and non-HLA induced AMR:-

- Acute microcirculatory inflammation as evidenced by [c+g+v>1] on biopsy
- DSA positive (MFI not specified, as there is recognition that circulating DSA's are likely to be lower post-transplant in some cases due to absorption by the graft)
- C4d +ve by immunofluorescence or immunohistochemistry

3.2Treatment

- Methylprednisolone (MP) 500 mg x 3 doses, followed by 30mg prednisolone (to follow a reduction dosing regimen, reduction regimen not specified but as per treating physician/surgeon preference)
- Plasma exchange (PLEX) X7 (course can be extended if there is evidence of ongoing inflammation and AMR)
- Intravenous Immunoglobulins x 2 doses of 1g/kg of ideal body weight adjusted dosing https://www.england.nhs.uk/wp-content/uploads/2019/03/PSS9-Immunoglobulin-Commissioning-Guidance-CQUIN-1920.pdf
- Rituximab 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
- Optimisation of baseline immunosuppression Diagrammatic representation:

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

*Methylprednisolone
**IVIg is to be dosed 1g/kg of ideal body weight adjusted dosing (max. 2g/kg)
IVIg has to be approved for use by the immunoglobulin panel and relevant form must be submitted prior to request supply from pharmacy.
Process to access ivig urgently/out of hours: http://insitetogether.xuhl-tr.nhs.uk/SP2007/Medicines%20Information/Procedure%20for%20out%20of%20hours%20Ig.pdf

Special considerations:

Check HIV, hepatitis B,C and TB (quantiferon) serology prior to administration of rituximab. Consent form prior to use of rituximab. Follow safety checklist prior to prescribing on rituximab chart (appendix 1).

3.3 DSA Monitoring:

DSA monitoring is currently done by Luminex which is a solid phase assay, Luminex was developed to be a qualitative assay and not a quantitative one and any interpretation of an antibody's Median Fluorescence Intensity should reflect this. Please check with the Head of Transplant Laboratory before requesting DSA. Antibody runs are done once per week (usually Wednesday) and a serum sample should reach the lab latest by Wednesday morning. For urgent results please contact H&I lab on ext. 4607. Below is a guide to DSA monitoring for patients that develop acute AMR

1. DSA at time of biopsy
2. After first round of PLEX (7 as per above protocol)
3. At end of AMR treatment to assess response

Subsequent DSA monitoring will be on an individual case by case basis.

3.4 Rationale:

3.4.1 Plasmapheresis

Plasmapheresis removes circulating DSA and is used in desensitisation protocols as well as in the treatment of AMR (4-6) . Different techniques used include plasma exchange and immunoadsorption.

Whilst historic observational studies had mixed conclusions on the benefit of plasmapheresis in the treatment of AMR, one of the few RCTs in the treatment of AMR by Bohmig et al, had to be terminated due to the significant benefit seen in the interventional arm receiving immunoadsorption (4, 5, 7-10). 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(11).

3.4.2 Intravenous immunoglobulin

IVIg has numerous potential effector mechanisms which could attenuate the treatment of AMR, these include the ability to neutralise circulating DSA, inhibition of complement activation and blocking immune activation by competing for FcγRs(12) . 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 (13). However, there is no significant evidence to show its efficacy for the indication of treating AMR when used in isolation. The only randomised control trial into the use of IVIg in allograft rejection is historic and pre- dates AMR as defined by Banff (14). In that particular study the researchers found that IVIg alone was equivalent to OKT3 in the treatment of steroid resistant rejection. Another 7 observational study published around the time, showed that the use of IVIg could improve the outcome in patients with both steroid and anti-lymphocyte antibody resistant rejection (15).

3.4.3 Rituximab [**Truxima**]

Biological agents targeting B-cells, plasma cells and their derivatives have been increasingly used as adjuvant therapy in both desensitisation and AMR treatment protocols over the past decade (4).
Rituximab and bortezomib having been the most extensively 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. Preliminary case reports and series suggested a benefit of the addition of rituximab to the standard treatment protocols of AMR. As such, rituximab is now the commonest add on agent used in the treatment of acute AMR (4, 16). However more recently two notable studies have emerged which may cast some doubt over the benefit of rituximab for the treatment of AMR. In the RCT, Ritux ERAH, which has published its one year outcomes, analysed the effectiveness of rituximab versus placebo in 38 patients with acute AMR receiving plasmapheresis, IVIg and corticosteroids. At one year, there was no benefit of adjuvant rituximab in terms of allograft; the study was underpowered (17). The longer term outcomes have yet to be reported.

4. 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.

5. Monitoring and Audit Criteria

Key Performance Indicator	Method of Assessment	Frequency	Lead
Incidence of AMR	Biopsy and information from Proton	Every 2 years	
1 year creatinine post AMR	Proton	Every 2 years	

6. 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

7.Supporting Documents and Key References

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8. Key Words

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

APPENDIX 1

University Hospitals of Leicester
Renal and Transplant Services

CONSULTANT

……

RITUXIMAB CHART
1g
One or two doses

PRESCRIBING, ADMINISTRATION AND MONITORING

Patient Name

Drug Sensitivities

Date recorded	*Drug*	*Reaction*

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	10mg 6hrly as required		

Date																
Time																
Dose																
Given/ 2nd Sig.																

Drug (approved name): **Hydrocortisone**

Route:	Dose/ Freq	Start Date	Sig:
IV	100-200mg		

Date																
Time																
Dose																
Given/ 2nd Sig.																

Drug (approved name): **Salbutamol**

Route:	Dose/ Freq	Start Date	Sig:
neb	2.5mg		

Date																
Time																
Dose																
Given/ 2nd Sig.																

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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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