ACUTE T CELL-MEDIATED REJECTION

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TABLE OF CONTENTS

ABBREVIATIONS

ACEi	angiotensin-converting-enzyme inhibitor
ABMR	antibody-mediated rejection
ARB	angiotensin receptor blockers
ATG	anti-thymocyte globulin
AZA	azathioprine
BKV	BK polyoma virus
CKD	chronic kidney disease
CMV	cytomegalovirus
DSA	donor-specific HLA antibodies
EBV	Epstein-Barr virus
IFTA	interstitial fibrosis and tubular atrophy
IS	immunosuppressant
IV	intravenous
IVIG	intravenous immunoglobulin
MMF	mycophenolate mofetil
MPA	mycophenolic acid
MPS	mycophenolate sodium
PJP	*Pneumocystis jiroveci* pneumonia
SRL	sirolimus
TCMR	T cell-mediated rejection
UTI	urinary tract infection

GUIDING PRINCIPLES

T cell-mediated rejection (TCMR) is the most common form of rejection post-transplant. It results from the alloimmune response to the kidney allograft and is an expected consequence of under-immunosuppression (IS). The hallmark is tubulointerstitial infiltration and damage to renal tubules that is progressive. It is associated with development of renal scarring (IFTA), development of donor-specific antibodies and risk of antibody mediated rejection (ABMR), loss of kidney allograft functional capacity and premature kidney allograft failure.

- TCMR is preventable with effective rejection prophylaxis using immunosuppressant medication.
- Stratification of TCMR-risk should be undertaken in all patients, with adjustment to screening and IS rejection prophylaxis tailored accordingly.
- TCMR may be clinically silent (subclinical) with no apparent change in serum creatinine from baseline.
- Diagnosis of TCMR requires histopathology obtained by kidney allograft biopsy. Surveillance biopsy can effectively identify subclinical TCMR.
- The mainstay of treatment of TCMR includes high-dose IV corticosteroids and intensification of baseline immunosuppression (rejection prophylaxis).
- Responsiveness to treatment is confirmed by resolution of histological features of TCMR on repeat kidney biopsy at 4-6 weeks after initiation of treatment.
- Additional measures to mitigate risk of IS side effects should be initiated at the same time as treatment for rejection.
- Additional prophylaxis against viral infection such as CMV and PJP may be required following treatment. BKV disease is addressed in separate guidelines.
- Following treatment of rejection, immunosuppressant treatment may be tapered, depending on the cause of rejection. Corticosteroids should not, however, be tapered to alternate-day dosing and should remain at a low daily dose indefinitely.
- Resolution of rejection is confirmed histopathologically with a follow-up biopsy.

ACUTE T CELL MEDIATED REJECTION GUIDELINES

RISK ASSESSMENT

1. Risk stratification – increased risk identification

- Increase in HLA mismatch at the class II HLA locus is associated with increased risk of TCMR and ABMR
- Patients with prior sensitization but without donor-specific antibodies and a negative flow cross-match are NOT as increased risk of TCMR, relative to similarly HLA matched recipients.
- Patients with a positive crossmatch or with a history of pre-existing donor specific antibody with a negative current cross-match are at increased risk of both TCMR and ABMR.
- Patients with systemic or kidney infections are at increased risk of TCMR, including episodes of CMV disease, BKV infection, allograft pyelonephritis.
- Patients with more rapid drug metabolism (younger age, genetic polymorphism) may be at risk for reduced IS drug exposure and therefore risk of TCMR.
- Patient having socio-demographic risk factors associated with non-adherence may be at increased risk: poverty, poor social support systems, adolescence, transfer to new care providers (e.g. to adult care), previous history of non-adherence.
- Patients consuming medications or food substances (e.g. grapefruit) that interact with CNI pharmacokinetics, or who are inconsistent about food consumption with medication dosing are at increased risk of variable or low drug exposure.
- Patients with prior episodes of TCMR are at increased risk of further episodes of TCMR
- Any reduction of IS, including planned tapering or for management of viral infection or adverse effects, increases the risk of TCMR.
- Complete withdrawal of IS is always associated with a high risk of TCMR and eventual allograft failure. IS prophylaxis for rejection is required for the life of the kidney allograft.

2. Surveillance for TCMR

- ***Serum creatinine*** is measured on regular blood test monitoring. Elevated serum creatinine >10% above baseline should indicate increased risk of TCMR but is non-specific. Creatinine is relatively insensitive to identify mild or indolent TCMR. It is also insensitive in children with excess functional capacity from a larger adult donor kidney. Rejection that is not associated with increased creatinine designated as “subclinical”. A low index of suspicion must be employed to indicate biopsy with any sustained and unexplained increase in creatinine from baseline.
- ***Surveillance biopsies*** have their greatest utility in the first 24 months after transplant. In the first 3-6 months, they are most effective for surveillance of subclinical rejection. At 12-24 months, they provide for ongoing rejection surveillance, but also identify later features of IF/TA, chronic inflammation (i-IFTA) and early antibody-mediated rejection.
- Regular ***screening for non-adherence*** is incorporated into the medication reconciliation history, included targeted questioning of the number of missed or late/early doses for the primary immunosuppressant medication in the last 7 days.
- ***Therapeutic drug monitoring*** is used for dosage adjustment, but over time the variability in trough primary immunosuppressant drug levels (coefficient of variance) is a useful indicator for inconsistent dosing or non-adherence. See TDM guidelines.

3. Interventions to mitigate risk

- ***Pharmacokinetic*** (PK) testing is used to optimize dosing in patients at baseline after transplant and those at increased risk for altered drug metabolism. PK testing identifies "slow metabolizers" who require higher trough level targets to obtain therapeutic drug exposure. Since trough monitoring has less utility, PK testing for MPA is needed to confirm the desired drug exposure. Usual pattern of food intake with medication should be replicated during PK testing. See TDM guidelines.
- Increased ***frequency of monitoring*** is often required to establish a pattern of non-adherence and risk of rejection. This may include increased frequency of blood testing, additional surveillance biopsies, or increased clinical contact.
- Increased ***supports*** – for families and patients flagged as increased risk for non-adherence. This may include social work, psychology and pharmacy intervention, as well as increased frequency of assessment in the clinic.

DIAGNOSIS

1. Kidney Biopsy - Grading of TCMR Severity

- TCMR is diagnosed on kidney allograft histology, obtained by kidney biopsy.
- All biopsies are graded according to the Banff classification (1-5).
- A grade of Banff 1A or greater indicates moderate to severe rejection.
- 'Borderline' is a grade of rejection that falls in a milder range of the spectrum of severity. It is associated with increased IFTA and reduced long-term allograft survival **(6-22)**. Within the borderline grade, there is also potentially a range of severity that may mandate individualization of treatment approach (e.g. i0t1, vs i1t3).
    - Cellular infiltrates have regulatory and cytotoxicity phenotypes that fall between Banff 1A grade and normal.
    - Chemokine markers of inflammation are increased in borderline grade.
    - Lack of treatment is associated with persistence of inflammation on follow-up biopsies.
    - Treatment is associated with histological improvement of acute inflammation and reduction in development of IFTA.
- Isolated tubulitis (i0t≥1) identifies tubular infiltrating mononuclear cells without significant associated interstitial inflammation. It technically falls within the spectrum of Borderline grade. The pathological significance is uncertain beyond identifying cognate interaction between recipient immune system and allograft.
- Isolated inflammation (i≥1t0) is uncommon and non-alloimmune sources of inflammation should be sought.
- Chronic inflammation is more recently being quantified by the i-IFTA score, which grades inflammation in chronically damaged (IF/TA) of renal cortex (4, 23). It is significantly associated with allograft failure (23-25). In combination with t2 level tubulitis in non-scarred cortex, it is graded as chronic, active TCMR. When i-IFTA is present and lesser tubulitis is identified (e.g. t1), this is considered "suspicious" for chronic, active TCMR.

2. Clinical Rejection – Increased Creatinine

- Suspected clinically if an acute increase in creatinine >10 % above baseline. An increase of >25% is highly suspicious (allograft AKI).
- First, rule out other causes for increased creatinine:
    - Structural renal disease like obstruction, renal artery stenosis, leak, compression by hematoma
    - Infection: CMV, BKV, pyelonephritis or other systemic infection
    - Volume depletion: intercurrent illness, salt wasting
    - Recurrent kidney disease
    - Medication nephrotoxicity: CNI, other medications

- A trial of volume repletion with IV normal saline may be used to correct suspected volume depletion (i.e. functional AKI), and should fully achieve the prior baseline GFR in order to be deemed successful.
- Unless a clear cause other than acute rejection is identified, patients should have a renal biopsy to rule out acute rejection.
- Carefully review recent history for non-adherence, which should result in high index of suspicion of rejection.
- Indirect signs that suggest the possibility of rejection include slow rise in creatinine over several months (creatinine creep), worsening hypertension, and soft signs of worsening tubular function: low grade anemia, metabolic acidosis, worsening hyperparathyroidism.

3. Sub-Clinical Rejection – No Increase in Creatinine

- Diagnosed on surveillance biopsy, in the *absence* of a significant change in the serum creatinine from baseline.
- Ongoing subclinical rejection may be identified on follow-up biopsies following treatment of rejection, even if there has been functional recovery of clinical rejection episodes.

4. Chronic rejection

- Chronic inflammation in the setting of IFTA should be considered as significant and indicates need for additional treatment (23-25).
- It may be identified on clinically indicated biopsies or on surveillance/follow-up biopsies where it may represent incomplete resolution of acute TCMR.

5. Other forms of rejection

- Management of other forms of rejection, such as ABMR will be dealt with separately
- Screening for evidence of co-morbid forms of rejection is needed at the time of diagnosis of TCMR and in the evaluation process.
- Patients with suspected TCMR should be screened for donor-specific HLA antibody (DSA).
- Histological evaluation of the kidney biopsy will identify glomerulitis, peri-tubular capillaritis, C4d staining or evidence of chronic transplant glomerulopathy, to indicate further treatment.

TREATMENT PLAN

The complete management of an episode of acute TCMR takes place over an 8-week period. The treatment plan is formulated based on the severity of acute rejection as determined by the histological stage, whether it is recurrent or steroid resistant, whether there is comorbid renal disease such as antibody-mediated rejection of polyoma virus infection, and the stage of chronicity. Additional clinical factors such as non-adherence are factored in as well.

The treatment program begins with admission for intravenous corticosteroids (3 daily doses) and then tapering of prednisone over a two-week period. Additional treatment is administered at the same time as the IV steroids, if indicated for severe or refractory disease. Baseline immunosuppression targets and drug dosing are adjusted. Adjunctive medications for infection prophylaxis and side effects are generally tapered after the first 4 weeks. Final decision on ongoing maintenance immunosuppression is made at 8 weeks, on review of results from the biopsy.

All grades of rejection, including borderline grade (i1t1 or greater), are considered for active treatment.

1. Initial Treatment of TCMR (Clinical or Subclinical Rejection)

- Rejection is treated based on the intensity of the histopathologic grade on biopsy, regardless of whether there was clinical indication for the biopsy, for surveillance or to follow-up prior treatment of rejection.
- Initiate treatment urgently with intravenous high dose methylprednisolone for 3 doses, and then taper dose over 14 days with oral prednisone (prednisolone). The initial dose of methylprednisolone is 300 mg/m^2 (max 500 mg) daily x3 days, and then 40 mg/m2 (max 60 mg) of prednisone (prednisolone) daily.
- In the setting of severe TCMR (i3t3), consider additional treatment with Thymoglobulin (26).
- Prednisone is tapered every 3 days until a minimum daily dose of 3 mg/m^2 (max 5 mg) is reached: 40, 20, 10, 5, 3 mg/m^2.
- Patients should remain on daily prednisone thereafter and should not be tapered to alternate day treatment. For patients early post-transplant, the previous tapering regimen should be resumed once the equivalent dose is reach on the rejection taper.
- Primary IS (tacrolimus or sirolimus) trough level target should be intensified by one level from the current target to achieve the desired therapeutic drug exposure (AUC_{0-12}; 110, 140, 170, 210 mcg*h/L).
- Increase primary IS dose by ~10-25% from previous in order to achieve the increased target range.
- Follow trough drug levels at least weekly until target is maintained on two consecutive weeks. This dose should be maintained until resolution of rejection is confirmed.
- Adjunctive IS (MMF, MPS, AZA) should also be optimized to achieve the optimal dosing for MPA [MMF: 600 mg/m^2 or MPS: 432 mg/m^2].
- MPA pharmacokinetics should be utilized to guide dosing, to achieve therapeutic drug exposure 45-60 mg*h/L or higher as tolerated.
- If patient is on AZA then consider switch to MPA drug class. If MPA is not tolerated, consider use of SRL as a secondary agent at lower dose (target 5-8).
- IVIG may be considered for treatment of TCMR when standard therapies are otherwise contraindicated, like in the setting of severe BK viremia, other active infectious complications or malignancy.

2. Isolated Tubulitis:

- Isolated tubulitis (i0 t≥1) has not been well defined in regard to pathogenicity and utility of treatment as rejection (27). Although within the Borderline grade, it may not require intensive treatment with IV methylprednisolone.
- A trial of intensified baseline immunosuppression may be warranted, such as when there is low-grade but non-trivial inflammation (e.g. 5-10%, i0), in the presence of donor specific antibody, or when it follows treatment for more severe acute rejection.
- Primary IS (tacrolimus or sirolimus) trough level target may be intensified by one level from the current target to achieve the desired therapeutic drug exposure (AUC_{0-12}; 110, 140, 170, 210 mcg*h/L).
- Adjunctive IS (MMF, MPS, AZA) should also be optimized to achieve the optimal dosing for MPA [MMF: 600 mg/m^2 or MPS: 432 mg/m^2].
- MPA pharmacokinetics should be utilized to guide dosing, to achieve therapeutic drug exposure 45-60 mg*h/L or higher as tolerated.
- If patient is on AZA then consider switch to MPA drug class.

3. Adjunctive Measures:

- Start gastrointestinal prophylaxis with ranitidine (3 mg/kg/dose BID; max 150 mg) for 14 days, then PRN
- Resume trimethoprim/sulfamethoxazole (5 mg TMP/kg/day once daily; max 80 mg TMP /day) for PJP prophylaxis for 28 days, then re-assess.

- Start or continue vitamin D25 (>1 yo: minimum 2000 units daily; 0-12 mo: 1000 units daily), and titrate dose according to vitamin D levels.
- Re-start valganciclovir prophylaxis (daily dose = 7*BSA*CrCl; max 900 mg) ***only if CMV risk is elevated*** (Recipient CMV IgG negative on current testing), and continue for 28 days.
  NOTE: Dosing by GFR is calculated using the Schwartz formula [eGFR = 36.5 x ht(cm)/SCr(µmol/L)], based on the renal function parameters on the day starting treatment.
- Target BP control to <90th %ile for manual BP while on corticosteroids.

4. Refractory Acute TCMR (Steroid Resistant)

Refractory acute TCMR is defined by persistence of Banff grade i1t1 or worse rejection on kidney biopsy. If serum creatinine in clinical TCMR continues to rise after 1-2 weeks of IV methylprednisolone and intensified immunosuppression, repeat urgent biopsy is indicated. Note that in subclinical TCMR, a creatinine rise (10-25%) may follow treatment of TCMR and does not necessarily indicate need for a biopsy. Otherwise, response to treatment is reassessed at the 2-month follow-up biopsy.

Diagnosis and grade of rejection is based upon histology of the kidney biopsy. Refractory TCMR is considered “clinical” if there is deteriorating renal function indicating biopsy, and “subclinical” if it is identified on the follow-up surveillance biopsy.

- In the case of ongoing, steroid-resistant rejection (i.e. following initial Rx with steroids), repeat treatment with intensified corticosteroids IV (600 mg/m^2 per dose x3 doses; max 1000 mg/dose), followed by prednisone taper.
- Further intensify baseline immunosuppressant medication. If PK not obtained to optimize MMF/MPA dosing, this should be strongly considered. Target MPA dosage to achieve AUC 45-60.
- Consider addition of thymoglobulin if follow-up biopsy confirms persistent or worsening rejection Banff grade 1A or worse. See below for dose recommendations.

5. Chronic, active rejection

Management of chronic, active rejection has yet to be well defined in the literature. It is considered pathogenic, based on association with functional decline and allograft failure. It may precede development of DSA. Chronic inflammation that is suspicious for chronic, active rejection (e.g. t1i-IFTA1) should also be considered for active treatment. Options for treatment include the following:

- Intensification of baseline prednisone dose at 5-10 mg/m^2
- Intensification of MPA to achieve therapeutic drug exposure 45-60 mg*h/L or higher as tolerated. If not previously performed, pharmacokinetics should be considered in order to optimize dosing,
- Addition of sirolimus in combination with reduced tacrolimus, to maintain similar overall drug exposure. Maintain TAC >5 and SRL >5, and adjust to keep the sum of trough levels <12.

6. Acute Vascular Rejection

- Vascular rejection is denoted by the acute Banff v-score >0.
- Screen for evidence of DSA. If present, treat as for antibody-mediated rejection (AMR).
- Consider concomitant Thymoglobulin and/or IVIG therapy with initial steroid pulse.

MEDICATION DOSING

Thymoglobulin

- Use the brand **Thymoglobulin (**antithymocyte globulin, rabbit), as per the product monograph. Administer initial dose slowly over 8-12 hours, and adjust infusion rate as

tolerated by patient. Thymoglobulin is superior to ATGAM (antithymocyte globulin, equine) for treatment of rejection (28).

- Empiric dosing recommendations are derived from existing guidelines (BCT induction) and are less than published clinical trials (28-31), which recommend between 10-14 days of treatment.
- Thymoglobulin dose: Initial dose 1.5 mg/kg (max 150 mg).
- Usual dosing is 5 days, for a total dose of 7.5 mg/kg.
- Alternative protocol: in cases where dose minimization is desired, dosing can be tailored to the achieved level of lymphocyte depletion (32). A minimum of three doses (4.5 mg/kg) is usually required. On day 4, 5 of treatment, T cell subsets can be measured to determine if subsequent doses are required (target CD3 count: <50 cells/mm^3) (33).
- Prescribe Thymoglobulin in addition to standard treatment for TCMR. For florid rejection, consider first day treatment with high-dose methylprednisolone only (i.e. day 0), and start Thymoglobulin with the second dose of steroids on day 1.

Administration

- Use a PICC line or temporary central venous catheter to administer.
- Hold all anti-hypertensive medications prior to infusion.
- Use premedication, starting 30 minutes prior to Thymoglobulin infusion:
  - Hydrocortisone IV (2 mg/kg, max 100 mg)
  - Diphenhydramine IV (1 mg/kg, max 50 mg)
  - Acetaminophen PO (15 mg/kg, max 1000 mg).
  - Ondansetron PO 0.2 mg/kg (max 8 mg).
- The acetaminophen dose should be repeated after 4 hours x1, and then continued every 4 hours PRN (max 4 doses per 24h).
- If treating concurrently with high-dose IV methylprednisolone, then substitute the treatment dose of methylprednisolone instead of hydrocortisone, and administer prior to IVIG as pre-medication

Monitoring

- Determination of CD3 counts (order B & T cell subset testing) is used to judge efficacy of T cell depletion, and should be obtained following completion of treatment.
  - Obtain B & T cell subsets at baseline prior to starting Thymoglobulin, and after completion of treatment.
  - If using alternative protocol, obtain repeat B & T cell subsets after the third dose of Thymoglobulin. Additional daily measurement is needed subsequently, if dosing to CD3 count target.
- NOTE: Indicate “post-thymoglobulin” on the lab testing requisition so that the lab is aware of the clinical status. Notify the immunology lab on the morning of follow-up testing to obtain same-day results.
- Repeat testing of subsets is performed on week 12 and then every 3 months until they have normalized.
- Active viral screening for BKV, EBV, CMV every 2 weeks is reinstituted for 8 weeks then monthly, to identify early viral risk.

Adjunctive treatment

- CMV prophylaxis is reinstituted for R+ patients for 3 months.
- PJP prophylaxis is reinstituted for 3 months post-treatment.

Intravenous Immune Globulin (IVIG)

- Total dose 2-4 g/kg over 7-10 days (34-36).These reports recommend using 0.5 mg/kg/dose, daily over 7 days
- Use in addition to standard treatment for TCMR.
- Alternative protocol: Give in divided doses (i.e. 0.5 g/kg weekly) over 6-8 weeks, to reduce risk of nephrotoxicity.

- NOTE: As there are many IVIG products available in the hospital, consider discussing with our local lab the use of non-sucrose based formulations to lower the risk of AKI.

MONITORING

Laboratory monitoring takes place on a weekly basis for at least the first 2-4 weeks, in order to monitor the effect of treatment, side effects and to titrate to immunosuppressant drug targets. Patients are evaluated in Transplant Clinic every two weeks for a total of 8 weeks, unless clinical issues dictate need for more frequent assessment. At 4 weeks in conjunction with the clinic visit, some patients will require pharmacokinetic testing for MMF and tacrolimus, to optimize drug dosage. A repeat biopsy is planned at 6-8 weeks and results are reviewed at the 8-week clinic visit.

1. **Clinic surveillance**
   - Clinic visit will occur in 2-4 weeks after treatment, based on severity of rejection and comorbidity Some visits may be completed while the patient is admitted for other reasons.

2. **Surveillance biopsy**
   - Patients are scheduled for follow-up surveillance biopsy in 6-8 weeks after initiation of treatment.
   - Persistent changes suggesting rejection should be treated as per protocol for treatment resistant rejection (above).

3. **Monitoring renal function**
   - Serial creatinine measurement on a minimum weekly basis is required for surveillance of further functional deterioration for the first 2 weeks.
   - Further decline in kidney function should prompt repeat kidney biopsy for diagnosis.
   - Return of creatinine to baseline following treatment is NOT a sufficient indicator of full response to treatment.
   - Mild increase in creatinine may be expected if treatment with ACEi is initiated, and does not necessarily indicate need for biopsy.

4. **Infectious surveillance**
   1. Screen for unsuspected UTI at the time of treatment initiation with u/a, urine culture and sensitivity.
   2. Screen for unsuspected viremia normally done at the time of biopsy. If *not done recently*, screen for CMV, EBV, BKV by PCR at the start of treatment with IV methylprednisolone.
   3. Monitoring of CMV, EBV, BKV PCR titers every 2 weeks for 2 months, then resume routine monitoring depending on patient risk profile.

5. **Therapeutic drug monitoring**
   - ***Consultation with Pharmacist*** at the time of admission for rejection treatment, and then follow-up as needed in clinic. Assessment should include screen for non-adherence, intake of medications or foods that may interact with CNI metabolism, and inconsistent timing of food intake (fasting vs. not) relative to CNI doses.
   - When inconsistent fasting/non-fasting behaviour is associated with the CNI dosing, the recommendation should be to favour fasting with each dose.
   - Serial monitoring of primary IS drug trough levels should continue on a minimum weekly basis until the target drug level is reached.
   - Prior excess variability in trough drug levels is an indicator of potential drug non-adherence.
   - Continue intensified primary IS until after confirmation of resolution of rejection, then consider tapering.

6. Pharmacokinetic testing for MPA

- For dose optimization, consider MPA pharmacokinetics (abbreviated) at ~4 weeks after treatment for rejection, after optimization of MPA dosing and completion of the prednisone wean.

7. Psychosocial, behavior and adherence

4. ***Consultation with the Psychologist and Social Worker*** at the time of admission for rejection treatment, and then follow-up as needed in clinic.
5. Screening and assessment of psychosocial risk factors is needed to identify risks associated with non-adherence, or changes in the stability of patient and family supports.
6. Patients should be screened for behavior changes or sleep disturbance that may result from treatment with high-dose corticosteroids.
7. Patients should be screened for excess or maladaptive response to the stress/trauma associated with an unexpected and serious diagnosis, and brief intervention planned accordingly.
8. Additional screening is indicated to assess for anxiety or maladaptive response associated with the stress from treatment of rejection.

8. Nutrition

- ***Consultation with the Dietitian*** at the time of admission for rejection treatment, and then follow-up as needed in clinic.
- Screening for dietary risk factors including weight gain associated with corticosteroids and calcium/vitamin D intake for risk of bone disease.

9. Bone health assessment

- Treatment with corticosteroids may be associated with loss of bone mineral content. This may be exacerbated by vitamin D insufficiency.
- Obtain a Dietitian consult with admission (see below)
- Check vitamin D25, Ca, PO4 and PTH levels on admission for steroid infusion to establish a baseline.
- Supplement with vitamin D, minimum 2000 units daily (1000 units for children age 0-12 months), until normal vitamin D stores confirmed. Adjust the dose according to vitamin D levels.

DISPOSITION

Resolution of rejection is determined by assessment of the follow-up biopsy. Complete resolution is typified by disappearance of inflammation as determined by Banff scores: t, i, ti, ptc, i-IFTA with each of these scores at zero (0) denoting complete resolution.

- If there are changes consistent with acute AMR (g>0, C4d staining) or transplant glomerulopathy (cg>1), then refer to the AMR guideline for disposition
- The finding of IF/TA in of itself does not modify disposition of treatment for rejection, however chronic inflammation within IF/TA (i.e. i-IFTA) is considered pathogenic.
- If there is evidence of biopsy of co-morbid glomerular disease (e.g. recurrence) or infection (e.g. BK virus), then refer to the guidelines for these specific problems for disposition after rejection has resolved.

1. Optimization of secondary immunosuppression

Prior to tapering the primary immunosuppressant, dosage of the secondary agent must be optimized.

- For MMF/MPS, this means targeting the dosage empirically recommended for treatment, or based on target AUC from PK studies. In patients with prior rejection, therapeutic drug exposure should continue to target MPA $AUC_{0\text{-}12}$ of 45-60 mg*h/L.
- Sirolimus may be considered an alternative to MMF/MPS in the setting of drug intolerance, but must be titrated to its effective dose prior to tapering of tacrolimus dose to target.

- Azathioprine is a second alternative, but may not provide sufficient adjuvant immunosuppression in patients who have manifest increased risk of rejection. In such cases, maintenance of second-level target immunosuppression (e.g. TAC target 6-10) should be considered.

2. Complete resolution

Ongoing rejection should be treated actively, unless there is contraindication to use of intensified immunosuppression.

- In the setting of complete resolution (t0, i0, ti0, ptc0), then augmented primary immunosuppression (i.e. tacrolimus or sirolimus) is ***tapered three (3) months following the biopsy*** to the next treatment threshold toward baseline (e.g. TAC target 5-8).
- For patients starting at treatment threshold above the 6-10 range, taper the target then every three (3) months until the baseline immunosuppression level is achieved.
- In the setting of ongoing, isolated tubulitis (i0t≥1), sustained intensification of immunosuppression may be warranted for 6-12 months or until resolution is documented on a subsequent biopsy.

3. Failure to conclusively confirm resolution

In some cases (e.g. AV malformation) it may not be possible to safely perform surveillance biopsy, particularly in the setting where clinical indicators suggest no further deterioration of kidney function.

- The primary immunosuppression should be continued at enhanced targets for a full 6 months after the start of treatment from the last biopsy.
- The primary clinical indicator in such cases will be change in serum creatinine over time. Stability of renal function is determined by the rate of change in creatinine in months 4, 5, and 6 post-treatment. Rising creatinine should prompt need for indication biopsy to exclude the possibility of ongoing rejection.
- In the absence of rising creatinine as above, then the primary immunosuppression may be tapered to baseline in a step-wise fashion every 3 months.

RELATED DOCUMENTS:

BCC Induction and Rejection Taper.xls – spreadsheet for dose calculation

Acute Kidney TCMR Comprehensive Management Order Sets - standard order sheet for coordination of hospital and outpatient treatment of rejection

REFERENCES

1. Solez K, Colvin RB, Racusen LC, Haas M, Sis B, Mengel M, et al. Banff 07 classification of renal allograft pathology: updates and future directions. AmJTransplant. 2008;8(4):753-60.
2. Haas M, Sis B, Racusen LC, Solez K, Glotz D, Colvin RB, et al. Banff 2013 meeting report: inclusion of c4d-negative antibody-mediated rejection and antibody-associated arterial lesions. Am J Transplant. 2014;14(2):272-83.
3. Mengel M, Sis B, Haas M, Colvin RB, Halloran PF, Racusen LC, et al. Banff 2011 Meeting report: new concepts in antibody-mediated rejection. Am J Transplant. 2012;12(3):563-70.
4. Haas M, Loupy A, Lefaucheur C, Roufosse C, Glotz D, Seron D, et al. The Banff 2017 Kidney Meeting Report: Revised diagnostic criteria for chronic active T cell-mediated rejection, antibody-mediated rejection, and prospects for integrative endpoints for next-generation clinical trials. Am J Transplant. 2018;18(2):293-307.
5. Loupy A, Haas M, Solez K, Racusen L, Glotz D, Seron D, et al. The Banff 2015 Kidney Meeting Report: Current Challenges in Rejection Classification and Prospects for Adopting Molecular Pathology. Am J Transplant. 2017;17(1):28-41.
6. Meehan SM, Siegel CT, Aronson AJ, Bartosh SM, Thistlethwaite JR, Woodle ES, et al. The relationship of untreated borderline infiltrates by the Banff criteria to acute rejection in renal allograft biopsies. JAmSocNephrol. 1999;10(8):1806-14.
7. Heilman RL, Nijim S, Chakkera HA, Devarapalli Y, Moss AA, Mulligan DC, et al. Impact of acute rejection on kidney allograft outcomes in recipients on rapid steroid withdrawal. J Transplant. 2011;2011:583981.
8. Akira K, Imachi M, Hashimoto T. Investigations into biochemical changes of genetic hypertensive rats using 1H nuclear magnetic resonance-based metabonomics. HypertensRes. 2005;28(5):425-30.
9. Saad R, Gritsch HA, Shapiro R, Jordan M, Vivas C, Scantlebury V, et al. Clinical significance of renal allograft biopsies with "borderline changes," as defined in the Banff Schema. Transplantation. 1997;64(7):992-5.
10. Schaier M, Seissler N, Becker LE, Schaefer SM, Schmitt E, Meuer S, et al. The extent of HLA-DR expression on HLA-DR(+) Tregs allows the identification of patients with clinically relevant borderline rejection. Transplant international : official journal of the European Society for Organ Transplantation. 2013;26(3):290-9.
11. Thierry A, Thervet E, Vuiblet V, Goujon JM, Machet MC, Noel LH, et al. Long-term impact of subclinical inflammation diagnosed by protocol biopsy one year after renal transplantation. AmJTransplant. 2011;11(10):2153-61.
12. Schaub S, Nickerson P, Rush D, Mayr M, Hess C, Golian M, et al. Urinary CXCL9 and CXCL10 levels correlate with the extent of subclinical tubulitis. AmJTransplant. 2009;9(6):1347-53.
13. Hruba P, Brabcova I, Gueler F, Krejcik Z, Stranecky V, Svobodova E, et al. Molecular diagnostics identifies risks for graft dysfunction despite borderline histologic changes. Kidney Int. 2015;88(4):785-95.

14. Moreso F, Ibernon M, Goma M, Carrera M, Fulladosa X, Hueso M, et al. Subclinical rejection associated with chronic allograft nephropathy in protocol biopsies as a risk factor for late graft loss. AmJTransplant. 2006;6(4):747-52.
15. Aoun B, Decramer S, Vitkevic R, Wannous H, Bandin F, Azema C, et al. Protocol biopsies in pediatric renal transplant recipients on cyclosporine versus tacrolimus-based immunosuppression. Pediatr Nephrol. 2013;28(3):493-8.
16. Birk PE, Stannard KM, Konrad HB, Blydt-Hansen TD, Ogborn MR, Cheang MS, et al. Surveillance biopsies are superior to functional studies for the diagnosis of acute and chronic renal allograft pathology in children. PediatrTransplant. 2004;8(1):29-38.
17. Dahan K, Audard V, Roudot-Thoraval F, Desvaux D, Abtahi M, Mansour H, et al. Renal allograft biopsies with borderline changes: predictive factors of clinical outcome. Am J Transplant. 2006;6(7):1725-30.
18. Gaber AO, Moore LW, Alloway RR, Woodle ES, Pirsch J, Shihab F, et al. Acute rejection characteristics from a prospective, randomized, double-blind, placebo-controlled multicenter trial of early corticosteroid withdrawal. Transplantation. 2013;95(4):573-9.
19. Wu K, Budde K, Lu H, Schmidt D, Liefeldt L, Glander P, et al. The severity of acute cellular rejection defined by Banff classification is associated with kidney allograft outcomes. Transplantation. 2014;97(11):1146-54.
20. Dart AB, Schall A, Gibson IW, Blydt-Hansen TD, Birk PE. Patterns of chronic injury in pediatric renal allografts. Transplantation. 2010;89(3):334-40.
21. Kee TY, Chapman JR, O'Connell PJ, Fung CL, Allen RD, Kable K, et al. Treatment of subclinical rejection diagnosed by protocol biopsy of kidney transplants. Transplantation. 2006;82(1):36-42.
22. Ho J, Rush DN, Karpinski M, Storsley L, Gibson IW, Bestland J, et al. Validation of urinary CXCL10 as a marker of borderline, subclinical, and clinical tubulitis. Transplantation. 2011;92(8):878-82.
23. Nankivell BJ, Shingde M, Keung KL, Fung CL, Borrows RJ, O'Connell PJ, et al. The causes, significance and consequences of inflammatory fibrosis in kidney transplantation: The Banff i-IFTA lesion. Am J Transplant. 2018;18(2):364-76.
24. Halloran PF, Matas A, Kasiske BL, Madill-Thomsen KS, Mackova M, Famulski KS. Molecular phenotype of kidney transplant indication biopsies with inflammation in scarred areas. Am J Transplant. 2019;19(5):1356-70.
25. Nankivell BJ, Shingde M, Keung KL, Fung CL, Borrows RJ, O'Connell PJ, et al. The causes, significance and consequences of inflammatory fibrosis in kidney transplantation: The Banff i-IFTA lesion. Am J Transplant. 2017.
26. Webster AC, Wu S, Tallapragada K, Park MY, Chapman JR, Carr SJ. Polyclonal and monoclonal antibodies for treating acute rejection episodes in kidney transplant recipients. Cochrane Database Syst Rev. 2017;7:Cd004756.
27. Nankivell BJ, P'Ng CH, Chapman JR. Does tubulitis without interstitial inflammation represent borderline acute T cell mediated rejection? Am J Transplant. 2019;19(1):132-44.
28. Gaber AO, First MR, Tesi RJ, Gaston RS, Mendez R, Mulloy LL, et al. Results of the double-blind, randomized, multicenter, phase III clinical trial of Thymoglobulin versus Atgam in the treatment of acute graft rejection episodes after renal transplantation. Transplantation. 1998;66(1):29-37.

29. Shenoy M, Roberts D, Plant ND, Lewis MA, Webb NJ. Antithymocyte treatment of steroid-resistant acute rejection in renal transplantation. Pediatr Nephrol. 2011;26(5):815-8.
30. Zarkhin V, Li L, Kambham N, Sigdel T, Salvatierra O, Sarwal MM. A randomized, prospective trial of rituximab for acute rejection in pediatric renal transplantation. Am J Transplant. 2008;8(12):2607-17.
31. Theodorakis J, Schneeberger H, Illner WD, Stangl M, Zanker B, Land W. Aggressive treatment of the first acute rejection episode using first-line anti-lymphocytic preparation reduces further acute rejection episodes after human kidney transplantation. Transplant international : official journal of the European Society for Organ Transplantation. 1998;11 Suppl 1:S86-9.
32. Midtvedt K, Fauchald P, Lien B, Hartmann A, Albrechtsen D, Bjerkely BL, et al. Individualized T cell monitored administration of ATG versus OKT3 in steroid-resistant kidney graft rejection. Clin Transplant. 2003;17(1):69-74.
33. Clark KR, Forsythe JL, Shenton BK, Lennard TW, Proud G, Taylor RM. Administration of ATG according to the absolute T lymphocyte count during therapy for steroid-resistant rejection. Transplant international : official journal of the European Society for Organ Transplantation. 1993;6(1):18-21.
34. Luke PP, Scantlebury VP, Jordan ML, Vivas CA, Hakala TR, Jain A, et al. Reversal of steroid- and anti-lymphocyte antibody-resistant rejection using intravenous immunoglobulin (IVIG) in renal transplant recipients. Transplantation. 2001;72(3):419-22.
35. Casadei DH, del CRM, Opelz G, Golberg JC, Argento JA, Greco G, et al. A randomized and prospective study comparing treatment with high-dose intravenous immunoglobulin with monoclonal antibodies for rescue of kidney grafts with steroid-resistant rejection. Transplantation. 2001;71(1):53-8.
36. Casadei D, Rial M, Raimondi E, Goldberg J, Argento J, Haas E. Immunoglobulin i.v. high dose (IVIgHD): new therapy as a rescue treatment of grafted kidneys. Transplant Proc. 1996;28(6):3290-1.

DOCUMENT HISTORY

VERSION	EFFECTIVE DATE	WRITER	REASON
00	11 Nov 2014	TBH	Initial creation of guideline
01	19 Mar 2015	TBH	Update with references
02	15 May 2015	TBH	Update with disposition after resolution
03	01 Jun 2015	TBH	Update for baseline pred dose and taper
03.1	03 Dec 2015	TBH	Updated borderline section with references
03.2	16 Feb 2018	SA, KH, TBH, SV	Update thymoglobulin, IVIG and steroids for refractory TCMR

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