BK Polyomavirus Interstitial Nephritis in Renal Transplant UHL Renal Transplant Guideline

1. Background

BK virus interstitial nephritis (nephropathy) occurs in approximately 3 to 8% of renal allografts. One ye ar graft loss is 35 to 67% and there is no therapy of proven efficacy. The clinical features of BK virus nephropathy mimic acute rejection although peak incidence is 10 to 13 months post transplant. It has however been reported as early as 8 weeks and as late as 5 years post transplant. Allograft dysfunction may be acute or slowly progressive.

Risk factors include: heavy immunosuppression (but no association with particular drugs has been identified), older age, diabetes mellitus, white ethnicity, male gender[1]. Previous acute rejection and pulse methylprednisolone treatment are associated with future development of BK virus nephropathy [2].

Urinalysis reveals low grade proteinuria and pyuria/microscopic haematuria. Urine cytology may identify "decoy cells". These are not specific for BK virus nephropathy (CMV and adenovirus infection have similar effects) and their absence does not rule out BK nephropathy.

Quantitative PCR of blood for BK virus DNA with viral loads of >10000 copies/ml is 100% sensitive and 88% specific for BK virus nephropathy[2]. Urine BKV PCR has a very low positive predictive value (27%) and its use is not cost effective. Hence do not test urine for BKV using PCR.

Renal histology: Features are very similar to those seen in acute cellular rejection i.e. interstitial mononuclear cell infiltrate, tubular injury and tubulitis. However, the presence of intra-nuclear basophilic inclusions in tubular epithelial cells on light microscopy, viral inclusion bodies on electron microscopy and positive SV40 large T antigen staining on immunohistochemistry help to differentiate. Clearly, differentiating BK virus nephropathy from acute rejection is important since inappropriate additional immunosuppression for acute rejection may precipitate accelerated graft loss in BK virus nephropathy. Late diagnosis of BKVN and chronic damage on allograft biopsy is associated with poor allograft survival[3]. Resolution of histological findings of BKVN can occur if BKVN is diagnosed early[4].

The cornerstone of treatment for BK virus nephropathy is reduction in immunosuppressive therapy. Pre-emptive reduction in immunosuppressive therapy guided by screening has been shown to be effective[5, 6]. The cost and logistics of a screening program is a challenge. Other adjunct therapies such us cidofovir [7] or leflunomide[8] are used in resistant cases but the evidence base for such treatment is very poor. A systematic review had shown no benefit on graft function by adding adjunct therapies[9].

A modification of immunosuppressive protocol with minimisation according to immunological risk has be en proposed at Leicester to reduce the burden of cumulative immunosuppressive therapy. This appro ach may in itself without requirement of regular screening bring down the incidence of BK Virus nephropathy and other viral diseases.

2. Scope

This guideline is to help medical, nursing and pharmacy staff managing patients undergoing renal transplantation.

Clinical guidelines are 'guidelines' only. The interpretation and application of clinical guidelines will remain the responsibility of the individual practitioner. If in doubt consult a senior colleague or expert.

3. Recommendations, Standards and Procedural Statements

3.1 Diagnosis and Treatment of a suspected case of BK Virus Nephropathy:

BK virus nephropathy should be considered in patients with a gradual decline in renal function post one year following renal transplantation and who are either have a contraindication for transplant biopsy or are unwilling for a biopsy. Patient within first year post transplantation should have an allograft biopsy to rule out rejection.

- **Plasma BKV PCR should be send urgently.**

- **If BKV PCR positive in context of rise in serum creatinine**
  - > 10,000 – presumptive diagnosis – Treat as BKVN
  - 5000 – 10,000 and rising trend – treat as BKVN & consider biopsy
  - <5,000 – Confirmatory renal biopsy before treating as BKVN

Any further deterioration in renal function following a reduction in immunosuppression should prompt a biopsy to look for evidence of acute rejection or other causes of dysfunction. All biopsies performed for investigating a decline in allograft function should have immunohistochemistry for SV40 large T antigen.

3.2 Treatment of histologically confirmed BK Virus Nephropathy

Before commencing treatment, obtain a baseline blood BK virus quantitative PCR for assessment of response to treatment. The management plan should **always be discussed with a consultant**.

3.2.1 Reduction in immunosuppressive therapy

The aim is to suppress viral replication without triggering acute rejection.

- Discontinue the anti-metabolite (mycophenolate or azathioprine)
- Reduce calcineurin inhibitor (Target trough levels: Tacrolimus 4 to 6ng/ml, cyclosporin 50 to 100ng/ml)
- Maintain low-dose prednisolone (<10mg/day)

Renal function should be monitored weekly initially and blood BK virus PCR for viral load should be performed monthly. Urine BK Virus PCR should not be used for monitoring.

Stabilisation of renal function may take up to 3 months to achieve with immunosuppression reduction alone. It is unusual to see renal function improvement even when viral replication is suppressed (ie renal impairment is irreversible). In addition between one to two thirds of patients have progressive allograft dysfunction in spite of immunosuppression reduction (and virological improvement).

A further deterioration in renal function following a reduction in immunosuppression should prompt a follow -up biopsy to look for evidence of acute rejection.

3.2.2 Treatment of concomitant acute rejection and BK Virus Nephropathy:

The treatment of recipients whose biopsy shows rejection with concurrent BKV nephropathy or early rejection after reduction of immunosuppression to treat BKV nephropathy remains problematic. An urgent SV40 Ag staining of the biopsy should be requested to differentiate interstitial nephritits from BKVN from acute rejection. **Treatment of such cases should always be discussed with the consultant**. A short course of pulse methylprednisolone is suggested. If it is steroid resistant, IVIg can be used.

3.3 Treatment of resistant cases of BK Virus Nephropathy:

If immunosuppression reduction does not lead to a fall in viral load to below 10000copies/ml within 12 weeks, or if renal function is rapidly deteriorating in the absence of any other identifiable cause, additional treatment may be considered.

It should be noted that this therapy is not licensed for this indication and the evidence supporting its use is derived from small case series at best. **The decision to commence this treatment must be discussed with the consultant** in charge and the patient must be fully informed of the rationale behind the treatment.

3.3.1 Leflunomide

Leflunomide is an anti-inflammatory drug approved for the treatment of rheumatoid arthritis. Leflunomide has considerable immunosuppressive potency in human renal and liver transplant recipients. It's active form has substantial antiviral activity against cytomegalovirus (CMV), herpes and BKV *in vitro* and in experimental animals. The rationale for the use of leflunomide in BK virus nephropathy rests on these combined immunosuppressive and antiviral actions.

In two large case series, the same research group reported on 26 and 17 patients, respectively, who developed BKVN on triple therapy with tacrolimus, MMF and steroids. In all patients, MMF was withdrawn and leflunomide was administered at a loading dose of 100 mg daily for 3-5 days followed by a

maintenance dose of 20-60 mg daily, aiming a trough level of 50-100ug/ml. Clearance or a progressive reduction in viral load and a stabilization or improvement of graft function was achieved in 84 and 88% of patients, respectively. The patients who deteriorated had leflunomide plasma levels <40 µg/ml.

Regimen:

- Immunosuppression reduction as above
- Loading dose of 100 mg daily for 3 days followed by maintenance dose of 20mg daily.

Side effects due to leflunomide are diarrhoea and rash, with potential for severe reactions including hepatotoxicity, pneumonitis, neurotoxicity, and bone marrow suppression in rare cases. Higher levels of leflunomide are associated with haemolysis and thrombotic microangiopathy.

3.3.2 Cidofovir

Cidofovir is a cytosine analogue DNA polymerase inhibitor licensed as 3rd line treatment for CMV retinitis. Case reports of benefit in patients with progressive multifocal leucoencephalopathy have suggested that it may have some activity against polyoma viruses.

It is nephrotoxic and induces proteinuria and renal failure in 20% of treated patients. Recently a low-dose regimen has been described that may be effective (stable renal function in all 8 patients treated with reduced immunosuppression and low-dose cidofovir (after mean 24 months) compared to 9/13 graft losses in those treated by immunosuppression reduction alone after mean of 8 months) and free of significant nephrotoxicity.

Regimen:

- Immunosuppression reduction as above
- 0.5 mg/kg cidofovir IV over 1 hour weekly for total of 4 to 10 doses depending on response. The dose can be increased to 1mg/kg/week if response is lacking.
- Before giving cidofivir, volume expand with 1L saline intravenously (after careful volume assessment of patient) over 1 hour. Probenecid pre-treatment is not necessary.

Cidifovir can induce neutropenia, and iritis/uveitis. Check FBC before each dose and monitor for development of ocular abnormalities.

4. Education and Training

No specific training issues identified.

5. Monitoring and Audit Criteria

Key Performance Indicator	Method of Assessment	Frequency	Lead
No. of new cases of BKVN per year	ilab data	Annual	Transplant nephrologists

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

Kidney; transplant; BK virus; immunosuppression; cidofovir; leflunomide

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DEVELOPMENT AND APPROVAL RECORD FOR THIS DOCUMENT		
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REVIEW RECORD			
Date	**Issue Number**	**Reviewed By**	**Description Of Changes (If Any)**
Feb 2008	1	Dr P Topham	Removal of leflunomide (no TAS approval)
Jan 2014	2	Dr P Topham	Leflunomide reinserted after approvasl by TAS
July 2016	3	Prof S Carr	Update references, add Algoritm, IVIG
Jan 2017	4	Prof S Carr	Updated and transferred to new template
July 2020	5	Gang Xu	Re ordered Leflunomide therapy as clinical usage is now more common.

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