BK Virus (BKV) Management Guideline: July 2017

BK virus has up to a 60-80% seroprevalence rate in adults due to a primary oral or respiratory exposure in childhood. In the immumocompromised renal transplant patient, BKV reactivation in the donor kidney could lead to viruria, viremia and nephropathy which could lead to graft failure.

Given the limited published studies on the management of BK virus, the following guideline outlines the current management considerations for BK viremia in British Columbia. However, individualized management made by the most responsible clinician(s) understanding the patient's immune and infectious risk is paramount.

General Principles:

- For patients with their first BK viral load in the detectable range, repeat viral load **1 week later** to verify result and establish that it is not rising rapidly. Once the patient has established BK viremia, monitoring more frequently than every second week (q2 weeks) is unlikely to change management.
- The therapeutic goal is to start the management protocol early to prevent the progression to BK nephropathy.
- The patient's primary transplant centre must be consulted for patients with complicated BK viral course (ie. those who do not rapidly clear BKV with reduction of immunosuppression and in whom further therapy is necessary or patients with a rise in serum creatinine).
- If increasing viral load and/or creatinine, perform renal biopsy (if not done already) and consult the patient's primary transplant center.
- IVIG infusion may be warranted for patients with concurrent rejection. This is a challenging management problem and should be co-managed with the primary transplant center
- The management considerations for pediatric patients may differ compared to adults, given their developing immune system, serologic status and pharmacodynamics to immunosuppressant therapy. These patients will be managed by the BC Children's Hospital Multi-Organ Transplant Program.
- For pediatric kidney recipients: Serologic testing for titre of BKV antibody in the recipient at the time of transplantation is suggested for stratification of infection risk and to guide treatment of incident BK viremia.

Monitoring and Management:

- Screen BK viral load q2 weekly for 16 weeks, then monthly until end of year two.
  (Except in patients who have ongoing viremia or have had viremia after the first year.)

- For screening of patients beyond year two
  - Continue screening monthly for 12 months from the last detectable BK viral load

- Screen all cases of unexplained acute rise in serum creatinine and at the time of renal biopsy.

- If viral load is **less than 1000 copies/mL:**
  - Continue screening at q2 weekly intervals. If this becomes a stable long term finding, monitor BK viral loads monthly.

- If viral load is **between 1000 and 5000 copies/mL:**
  - If viral load is within this range but rising (e.g. 1200 and one week later rises to 3500), reduce mycophenolate mofetil (MMF) or mycophenolate sodium dose by 50%.
  - Continue CNI (calcineurin inhibitor (cyclosporine/tacrolimus)).
  - Monitor BK viral load q2 weeks or monthly if stable.

- If viral load is **greater than 5000 copies/mL:**
    - Reduce MMF dose by 50%. If patient on steroid and rapidly rising viral load, consider stopping MMF. Repeat BK viral load q2 weeks.

    - If viral load continues to increase and patient is still on MMF:
        - **Routine Patient Scenario**: Stop MMF and continue CNI. Repeat BK viral load q2 weeks.
        - **High Risk Patient Scenario**: Stop MMF and continue CNI and **ADD** leflunomide for patients at high risk of rejection (e.g. transplant within 3 months, history of rejection or documented biopsy proven BKVN)
        - Repeat BK viral load q2 weeks.
    - If viral load continues to increase and patient is not on MMF, reduce CNI by 25-50%:
        - Target cyclosporine trough levels of 50-100 ng/mL or tacrolimus trough level of 3-4 ng/mL[1].
        - Add leflunomide, if not added already.
        - Repeat BK viral load q2 weeks.
    - If viral load continues to rise despite stopping MMF, reducing the CNI and adding leflunomide:
        - Stop CNI and **ADD** sirolimus.
        - Repeat BK viral load q2 weeks.

- If biopsy **proven BK virus nephropathy** (BKVN)
    - OPTION 1: Stop MMF, continue on CNI, **ADD** leflunomide
    - OPTION 2: Stop MMF and CNI, **ADD** sirolimus and leflunomide
    - Monitor viral load q2 weeks until stable viral load or undetectable.

- If increasing viral load and/or creatinine, perform renal biopsy (if not done already) and consult the patient's primary transplant center.

Therapeutic End Points:

- When viral load is **undetectable** for 2 readings:
    - If patient only reduced or stopped MMF, start adding or increasing MMF. Dose adjustments are made by 250 mg BID increments for MMF or 180 mg increments for mycophenolate sodium. Patients are rarely returned to full dose MMF. Often patients are maintained at 50-75% of their original dose. Continue to monitor q2 weeks for two months then monthly for one year.

    - If viral load remains less than 1000 copies/mL, continue to re-introduce MMF.

    - If viral load is over 1000 copies/mL, reduce or discontinue MMF and monitor q 2 weekly, following above protocol.

    - If the patient had any other changes to their immunosuppression regimen (e.g. reduction in CNI, addition of leflunomide or sirolimus), consult their **primary transplant centre** on how to re-introduce standard immunosuppression.

    - In addition to ensuring adequate immunosuppression, consider discontinuing leflunomide once the BK viremia has resolved and the patient is stable.

    - Ongoing BK management for patients with long term low levels of viremia should be co-managed with the primary transplant centre.

BK Viral Loads:

BK Viral Loads are run at St. Paul's Hospital in the virology lab from Monday to Friday. To get the fastest turnaround time for your centre, determine which day(s) your local laboratory ships specimens to St. Paul's Hospital. Blood will have to be drawn the day before as it needs to be frozen for shipping.

Leflunomide: There is only limited evidence for efficacy in BK viremia and BK nephropathy but the local experience has been favourable. As leflunomide has some immunosuppressant effects, treatment is often considered in conjunction with reduction in doses or changes to immunosuppression regimen.

Loading dose: 100 mg PO daily for 3 days. Patients should only be loaded when the BK viral load is rapidly rising or has established BK nephropathy. Otherwise, starting with the maintenance dose is appropriate for most patients.

Maintenance dose: 20 mg PO daily and titrate based on efficacy (BK VL reduction) and ADRs. Usual dose 20 to 60 mg PO daily. Sometimes every other day dosing is required due to side effects.

Drug Levels:

- **Routine drug level monitoring is <u>not</u> recommended based on current available evidence**. However, therapeutic drug monitoring may be of benefit in difficult situations when patients demonstrate a lack of therapeutic response or exhibit signs of drug toxicity.

    - A clear relationship between drug concentration and efficacy or toxicity is lacking for leflunomide, and its therapeutic range is not well established in the literature. In addition, steady state concentrations are achieved after 14-20 weeks of therapy[2] due to the drug's very long half-life. In contrast, efficacy and toxicity endpoints, such as renal function and BKV clearance, can be readily assessed in a timely manner.
    - Based on limited data, a therapeutic range for leflunomide's active metabolite (teriflunomide/A77 1726) is suggested to be trough levels of 40-100 mcg/mL
    - A mean trough level of 81.1 ± 14mcg/mL has been associated with a higher incidence of hemolysis. If drug level is indicated, suggest to check an initial level at least 2 weeks after starting therapy and then 1 month later to assess for stability and trend.

- If drug level for leflunomide is indicated (active metabolite A771 1726), send trough (pre-dose) sample to:

    Calgary Laboratory Services, #9, 3535 Research Rd. NW, Calgary AB, T2L 2K8, Phone: 403-770-3600
    (See sample requisition below)

Toxicity monitoring:

- CBC and differential, creatinine, AST, and ALT q4 weeks;
- Rash, diarrhea/GI upset

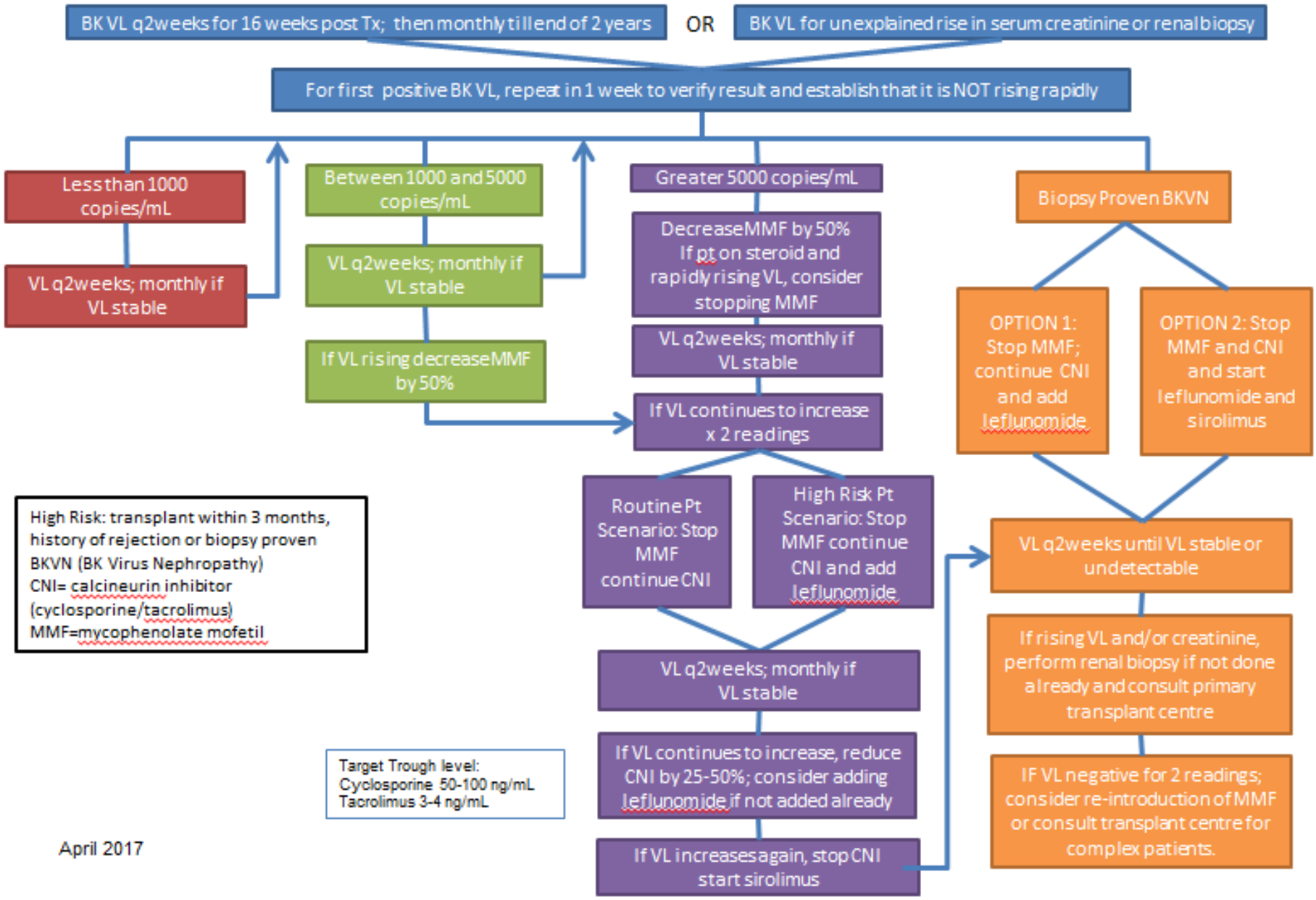
Contraindication:

- Pregnancy is contraindicated while taking leflunomide. Due to the extended half-life of the active metabolite, it may take several weeks/months to be eliminated. Contact the transplant clinic for more information.

1. Leca N, Muczynski KA, Jefferson JA, de Boer IH, Kowalewska J, Kendrick EA, et al. Higher levels of leflunomide are associated with hemolysis and are not superior to lower levels for BK virus clearance in renal transplant patients. Clin J Am Soc Nephrol. 2008 May;3(3):829–35.

2. Chong A, Zeng H, Knight D, Shen J, Meister G, Williams J, et al. Concurrent antiviral and immunosuppressive activities of leflunomide in vivo. Am J Transplant. 2006 Jan 1;6(1):69–75.

BK Viral Load (VL) Monitoring



Hospital Name: _____
Dept. of Pathology and Laboratory Medicine
Address: _____
_____
Phone: _____
Fax:_____

Leflunomide Level Instructions

Collection Date _____

Time_____

Collected by_____

Container: **RED TOP 1-3.5mL**
Test Code: **DISPO** – Leflunomide level

Special Instructions for Laboratory Staff

- allow blood to clot for approx 30min
- centrifuge at 1200g for 10min
- transfer serum to 12 x 75 aliquot tube (minimum volume required is 1 mL)
- freeze at **-20°C or colder**

Accessioned by:_____

Ship frozen sample on Dry Ice to:

Accession – DSC
Calgary Laboratory Services
#9, 3535 Research Rd. NW
Calgary AB, T2L 2K8
Phone: 403-770-3600

SEND THIS REQUISITION WITH THE SAMPLE

For Calgary Lab:
Please forward results to the phone/fax listed above: Attn:
_____