

2021

CLINICAL GUIDELINES FOR KIDNEY TRANSPLANTATION



Revised: Nov 2019

- AMR protocol update
- Induction protocol
- Management of the failed Kidney Transplant
- Hep B update

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1 Pre-Transplant

Kidney transplantation is the preferred treatment option for many patients who have or are developing end-stage renal disease and who are, or will be undergoing, chronic dialysis therapy. However transplant is not the best treatment for all patients.

1.1 PATIENT REFERRAL

Who Qualifies?

To potentially benefit from a transplant a patient should have:

- Progressive, irreversible renal disease
- No active malignancy or infection
- Absence of systemic disease which would severely limit rehabilitation
- Life expectancy greater than 5 years with a successful transplant
- Effective family or social support systems
- Willingness to comply with treatment and follow-up requirements

Eligibility Criteria

The BC Transplant program follows the published consensus guidelines of the [Canadian Society of Transplantation consensus guidelines on eligibility for kidney transplantation](#) *CMAJ - Nov 08, 2005*. Questions regarding a specific patient's potential eligibility should be referred to the appropriate transplant center.

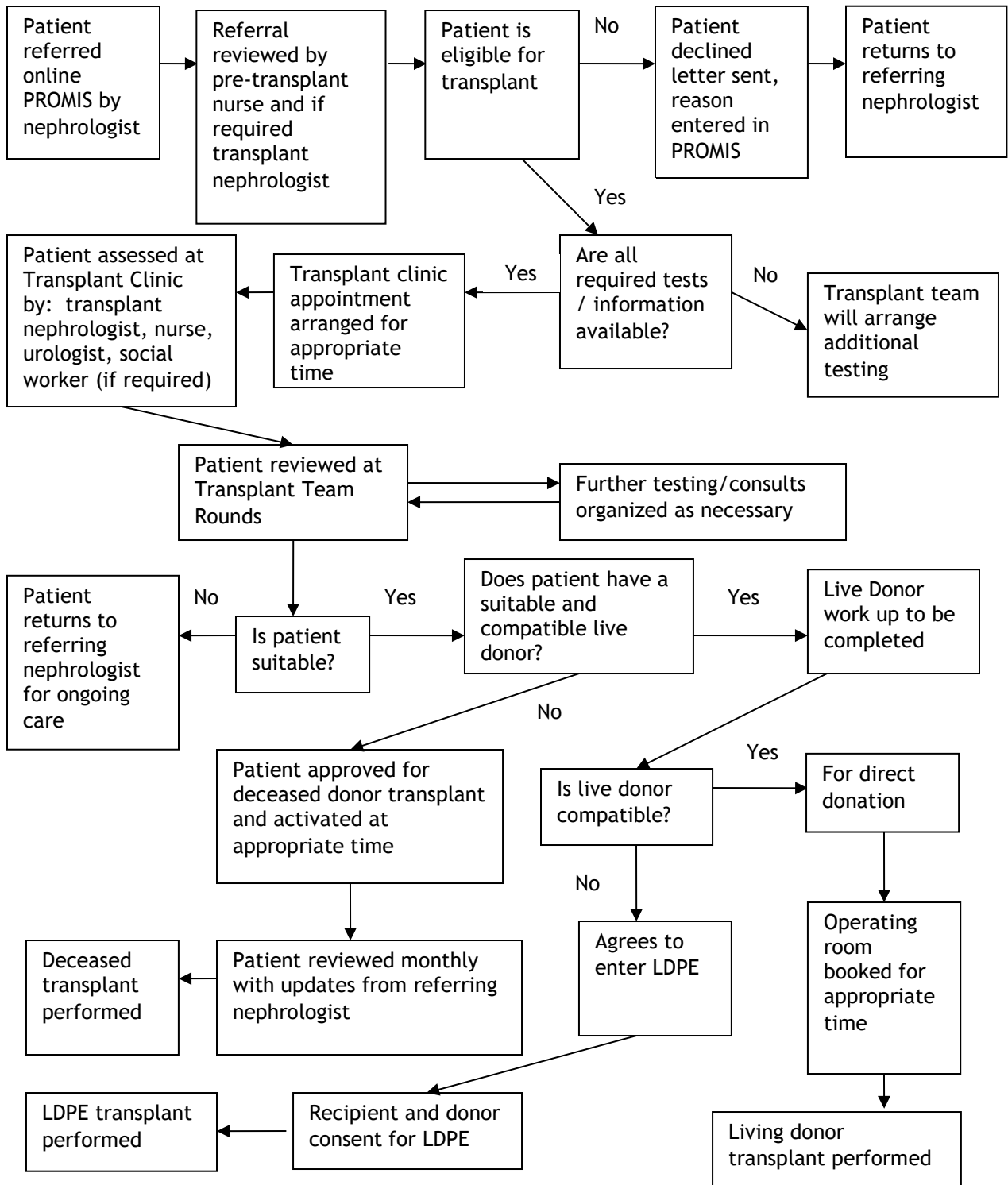
Referral

All referrals for kidney transplantation are made electronically through the PROMIS Kidney Transplant Referral module (See Figure 1). If you have any technical, training or support questions, contact the PROMIS support team: support@bcpra.ubc.ca or 604-806-8868. Referrals will be made to one of the three transplant centres in Vancouver: Vancouver General Hospital, St. Paul's Hospital or B.C.'s Children's Hospital (pediatric).

Absolute contraindications to transplant include:

- Active malignancy
- Severe respiratory conditions
- Severe Ischemic heart disease
- Severe peripheral vascular disease
- Transplant candidate with cirrhosis
- Severe cognitive impairment
- Active drug or alcohol addiction
- Patient non-adherence to therapy

Figure 1. Kidney Transplant Program Referral/Assessment



1.2 PATIENT ASSESSMENT

Once the patient has been referred to a transplant centre the patient is assessed by the transplant team. The routine evaluation includes consultation with members of the transplant team comprised of physicians, surgeons, clinical coordinator nurses (recipient and living donor) and a social worker. If clinically required, appointments are arranged with appropriate specialists from other disciplines.

During the assessment, patients and families receive written and visual information about transplantation which outlines:

- Transplant process
- Program options
- Risks and benefits (both live donor and deceased donor transplants)
- Medication regimen
- Lifestyle adjustments
- Effect of transplantation on existing medical conditions
- Temporary relocation to Vancouver (if required)
- Short and long term outcomes

Preliminary patient assessment investigations should be performed by the referring centre if possible. Testing that cannot be done locally can be arranged at the transplant centres. Patients who are on the active waiting list should have regular monitoring including cardiac testing and viral screening. The transplant centre will request regular updates and will review active patients depending on their clinical situation.

Patient Investigations:

The following routine investigations are reviewed during the assessment:

Laboratory
<ul style="list-style-type: none">• ABO• Complete Blood Count and platelet• Fasting blood Glucose• HLA Typing Class I and II• Multiscreen panel (Calcium, phosphate, alkaline phosphatase, AST, LDH, urea, creatinine, uric acid)• Electrolytes (sodium, potassium, chloride, CO₂)• Total bilirubin, direct bilirubin, albumin and total protein• Lipid studies (total cholesterol, triglyceride, LDL, HDL)
Urine
Midstream urine for culture and analysis
Micro / Serology
<ul style="list-style-type: none">• Hepatitis B, Hepatitis C, CMV, EBV, HIV, Varicella)
Radiology Studies
<ul style="list-style-type: none">• Chest X-ray• 12 lead Electrocardiogram• Mammography within 12 months for women over 50 years
Other
<ul style="list-style-type: none">• PSA (required for males over 45 years of age)• Recent PAP smear (within 6 months for adult females)

Additional tests are performed as required.

Cardiovascular Assessment

Cardiac disease is the leading cause of death following kidney transplantation. Cardiac death may be due to coronary artery disease or heart failure. All renal patients are at increased risk for cardiac disease because of their exposure to numerous risk factors including uremia itself. Thus all patients being considered for transplantation should be screened for coronary artery disease and cardiac dysfunction. The purpose of these investigations is twofold. First, to identify patients who have disease and would benefit from further treatment or, intervention prior to the transplantation in order to improve life expectancy after transplantation. The second purpose is to identify patients with advanced disease, in whom the perioperative and post-transplant risk is prohibitive so as to preclude transplantation.

All potential transplant candidates are at higher risk of coronary artery disease, but there are some very high-risk subgroups. High-risk subgroups include those patients with prolonged duration of dialysis (greater than 5 years), family history of coronary artery disease (CAD) in first degree relative, history of smoking, dyslipidemia (HDL less than 0.9 mmol/L, LDL greater than 3.4 mmol/L), body mass index (BMI) greater than 30, history of hypertension, and above all diabetes mellitus.

There is no ideal non-invasive screening test.

Useful tests include:

- Nuclear medicine myocardial perfusion imaging (MIBI) with exercise
- MIBI with persantine
- Echocardiography with exercise
- Echocardiography with dobutamine

Patients with a positive screening test should be referred to a cardiologist for further evaluation usually including coronary angiography. Suitable patients with critical disease should undergo intervention with bypass surgery or angioplasty and stenting. Some patients with severe diffuse disease will be turned down for transplantation because of their poor prognosis. If centres outside the Lower Mainland have difficulty in arranging cardiac testing the transplant centre will help facilitate testing and consults.

Vascular Assessment

All transplant candidates who have femoral bruits, claudication, or absent pedal pulses require a vascular assessment. This will be determined at the time of transplant evaluation by the Transplant Team physician or surgeon. Patients requiring vascular assessment may have iliac angiography with distal run-off or abdominal CT scan without contrast to assess degree of vascular calcification. The results will be reviewed by the Transplant Team. The outcome of the test will determine patient candidacy from a vascular perspective.

Hepatitis B

All patients will have screening for evidence of hepatitis B infection. This will include HbsAg, HbcAb and HbsAb. Patients who are HbcAb or HbsAg positive will have HBV DNA load determined. All patients who are HBV DNA positive will be referred to a Hepatologist for further testing and consideration of treatment. HBV infection is not necessarily a contraindication to transplantation but will depend on the severity of liver disease.

While waiting on the renal transplant waitlist, patients with hepatitis B infection will require:

- Annual liver panel and HBeAg
- Every 6 month HBV DNA
- Hepatology review at one year and two years

Hepatitis Testing:		Interpretation
HBsAg	Hepatitis surface antigen	HBV infection
HBcAB	Antibody to hepatitis B core antigen	Exposure to HBV infection may be active or inactive.
HBsAb	Antibody to hepatitis B Surface antigen	Immunity to HBV (vaccine induced or a result of prior infection)
HBV DNA	Hepatitis B viral load	Active replication of HBV
HBeAg	Hepatitis B e antigen	Marker of replication and infectivity
HBeAb	Antibody to Hepatitis B e antigen	Suggests viral clearing and recovery

All patients are tested for hepatitis B pre transplant: Patients who are HBsAg negative and HBsAB negative should be vaccinated against hepatitis B.

Patients who are HBsAg positive with HBV DNA positive replication prior to transplant should be referred to gastroenterology (GI)/hepatology for assessing the degree of liver disease and for antiviral therapy (pre transplant).

Pre transplant patients who are HBsAg positive and HBV DNA negative are inactive carriers (not actively replicating virus). These patients are at risk for reactivation of viremia and developing progressive liver disease triggered by immunosuppression after renal transplant. They should be reviewed by hepatology pretransplant to consider timing of treatment.

Patients who are HBcAB positive but are HBsAg and HBV DNA negative have cleared the virus from their blood but may still have latent virus in their liver. These patients are at risk for developing active Hepatitis B triggered by immunosuppression after renal transplant. These patients should be assessed and therapy considered on a case by case basis by GI/Hepatology.

BC Transplant covers the cost of **post-transplant** HBV antiviral agents for some recipients of liver and non-liver solid organ transplants depending on donor and recipient HBV core antibody status (in patients without active HBV replication) to avoid HBV reactivation with immunosuppressive therapy. HBV DNA testing should be done on all donors with HBV core antibody positive status.

This table refers to donors and recipients who are **HBsAg negative**. Generally, donors who are HBsAg positive would not be suitable donors, and recipients who are HBsAg positive would require life-long anti-viral therapy.

For living donor recipients, confirming immunity or immunizing to Hepatitis B is recommended prior to transplant.

Donor and Recipient: Hepatitis B Surface Antigen Negative (Oct 2019)

Organ Transplanted	Donor HBV Antibody Status	Recipient HBV Antibody Status	Anti-Viral Therapy Post Transplant
Liver	HBV core positive	HBV core positive or negative	Lamivudine for life
	HBV core negative	HBV core positive	Monitor for HBV reactivation* No prophylaxis
Non-liver	HBV core positive	HBV core negative (Regardless of HBV surface antibody status)	Monitor for HBV reactivation* No prophylaxis
	HBV core negative	HBV core positive	Monitor for HBV reactivation* May consider a referral to a hepatologist for ongoing monitoring

*Monitor for HBV reactivation at every 3 months for one year then every 6 months. If patient being treated for acute rejection, monitor for HBV reactivation every 3 months for 6 months. Tests to be done: liver enzymes, hepatitis B surface antigen, hepatitis B core antibody, hepatitis B surface antibody and hepatitis B DNA. If Hep B DNA detectable or HBsAg positive, consult transplant hepatology or infectious disease specialist.

Hepatitis C

All patients will be screened for evidence of hepatitis C infection. This will include anti hepatitis C antibody. Patients with a positive test will have testing for HCV RNA. Positive patients will be referred to a hepatologist for further evaluation and consideration of therapy. The degree of liver disease will be evaluated and this will normally include a liver biopsy. Patients with advanced disease i.e. cirrhosis will be turned down for transplantation.

While waiting on the cadaveric renal transplant waitlist, HCV positive patients require yearly:

- Liver panel
- HCV RNA quantitative
- Abdominal ultrasound
- CEA yearly
- Hepatology review

Patients who are HCV positive with viral replication may elect to be eligible to receive a kidney from a donor who is HCV positive. There is evidence that this does not result in a worse prognosis for these patients. Exceptional release will still be required at the time of the transplant (see [Section 3.8 Exceptional Distribution](#)).

HIV

HIV positivity is a relative contraindication for kidney transplantation. Some HIV positive patients are eligible for either a deceased or living donor kidney transplant. These patients must meet the following criteria outlined in the [Canadian Society of Transplantation consensus guidelines on eligibility for kidney transplantation](#) CMAJ - Nov 08, 2005.

- CD4+ T-cell count greater than 200 /mm³ for greater than 6 months
- Undetectable HIV-1 RNA for greater than 3 months
- On highly active antiretroviral therapy (HAART) for greater than 3 months
- Free from opportunistic infections

HIV positive patients who are placed on the deceased waiting list require close monitoring during the waiting period. Specific requirements and timing of testing decisions are made by the transplant team in conjunction with the infectious diseases team.

1.3 PRE-TRANSPLANT IMMUNIZATION

Viral infections are a common cause of post-transplant morbidity. Pre-transplant immunization is an effective strategy to decrease this risk. Immunization is most effective when performed prior to transplantation. All potential transplant recipients should have been immunized before transplant according to past immunization history. Antibody levels are determined at time of referral and patients are referred to public health for the appropriate vaccinations and boosters.

Patients should receive the following vaccinations prior to transplant:

- Td or Tdap
- IPV
- Hepatitis B
- Meningococcal (conjugate)
- Pneumococcal (conjugate and/or polysaccharide)
- Hib
- Influenza
- MMR
- Varicella

Live vaccines (MMR and varicella) administered before the transplant must be completed at least six weeks before transplantation.

Yearly influenza immunization is indicated for all immunosuppressed individuals.

Refer to: [BCCDC Communicable Disease Control, Immunization Program, Section III - Immunization of Special Populations](#)

1.4 TUBERCULOSIS TESTING

The tuberculosis (TB) screening questionnaire in PROMIS (in the monitoring section), is completed by the pre-transplant nurse. If the screening suggests this is a high risk patient an Interferon Gamma Release Assay (IGRA) test is arranged. This is done by BC Center for Disease Control (BCCDC). If the test is negative there is no treatment. If the test is positive the patient will be referred to their local community health clinic for TB treatment and monitoring. BCCDC provides documentation to the transplant centre during treatment and when TB treatment has been completed. See Appendix I: [PROMIS TB Screening Questionnaire](#)

1.5 PATIENT APPROVAL

When the assessment is complete, information about the patient is reviewed at a formal meeting of the Transplant Team. Patients that meet eligibility criteria are approved as candidates for transplantation. Complex cases are discussed at monthly city-wide renal meetings.

Patients who do not meet the eligibility criteria are turned down as potential transplant candidates. This decision and the date it occurred are recorded in the patient's file and in PROMIS. A letter outlining the reasons for non-acceptance is sent to the referring nephrologist, who normally communicates this decision to the patient.

At the time a patient is approved for transplant, an official acceptance form is signed by the transplant nephrologist and transplant surgeon and includes the date of this decision. The form becomes a permanent part of the candidate's medical chart. A formal letter of approval is sent to the referring nephrologist, transplant candidate, and a copy to the appropriate dialysis center and the general practitioner (GP).

Date of acceptance of transplant candidate does not determine place on waitlist. For waitlist purposes wait time begins on dialysis start date. Potential donors have extensive testing to ensure safety for donor and compatibility with recipient. Matched and suitable living kidney donors proceed with donation based on the time most suitable for the donor. See Appendix II, III [Kidney Transplant Clinic Deceased Donor Wait List and Agreement](#)

There are three options for the type of transplant donors a recipient may receive:

1. **Living donor:** Provides excellent health of a donor kidney, improved long term survival, and the ability to receive a transplant in a timely manner. The live donor is usually a family member or a friend. Medical assessments are conducted to determine whether the donor is a compatible and healthy match for the transplant candidate. If there is matched living donor who has given informed consent, they are called a compatible pair. The time of transplant surgery is scheduled based on the availability and wish of the donor and the best possible health of the recipient and operating times available. Also See BCT Clinical Guidelines – [Living Donation Kidney](#)
2. **Paired Exchange:** Thirty percent of potential kidney donors are suitable but not compatible with the intended recipient. This means the donor's blood type is not compatible with the recipient's blood type or the recipient has antibodies that will reject that donor's kidney. Suitable kidney donors who are incompatible with their recipients will be given the option of entering into the Canadian Living Donor Paired Exchange Program (LDPE). This registry attempts to find exchange combinations so that the intended recipient can receive a compatible kidney and donor can donate to a compatible recipient.

The donor may have to travel to another transplant centre outside of British Columbia, within Canada for donation. There is funding assistance available for the donors to travel to the out of province transplant centre for organ donation. The recipient usually receives a LDPE in Vancouver. Refer to Canadian Blood Services [LDPE](#) website and the BCT Clinical Guidelines – [Living Donation Kidney](#) for further information.

3. **Deceased Donor:** Deceased donor transplant occurs when a kidney is donated by someone who has died very recently in hospital and the family and appropriate consent for donation has been given. Approved transplant candidates who do not have potential living donors are placed on a waiting list for these organs. See Appendix II and III [Kidney Transplant Clinic Deceased Donor Wait List and Agreement](#)

1.6 PATIENT STATUS WHILE WAITING

Condition Update Report

Activated patients must have a monthly Condition Update Report completed in PROMIS by the referring nephrologist. This report provides information on the pre-transplant patient's condition from the time of activation to the time of transplant. The purpose of the condition update report is for the referring nephrologist to monitor and report the following:

- Significant acute or ongoing complications or co-morbid events
- Admissions to the hospital or emergency room visits
- Blood transfusions
- Consultations with positive findings
- Infections, including the organism and therapy instituted

The Transplant Team programs reviews the reports regularly and may request further assessment. Patients with new medical issues may be placed on temporary hold of the transplant waitlist.

Re-Assessment

As the waiting time for a kidney transplant can be long, patients may be required to return to their transplant centre for reassessment as they move closer to the top of the list. Appropriate investigations may be ordered or repeated from the initial assessment.

On Hold Status – Patients with new medical issues

Patients with new medical issues will be placed on temporary hold on the transplant waitlist. For example, if a patient develops an infection, they would be placed on hold until the infection has cleared. The referring nephrologists must contact the transplant centre to notify them of the need to place a patient on hold. Patients placed on hold do not lose their place on the waitlist. Once their suitability has been re-established, the patient returns to their previous location on the waitlist. On hold lists are reviewed weekly by the pre-transplant coordinator. Patients are removed from hold as soon as the medical issue has resolved. Ongoing communication between the referring nephrologist and the transplant centre is necessary to ensure timely removal from waitlist hold.

Removing Patients Permanently from the Waitlist

During the lengthy waiting time for a kidney transplant, a patient's condition may change to the point where they are no longer suitable for transplantation. Before a patient is removed from the waiting list, the following occurs:

- All relevant information is obtained from key sources such as the referring nephrologist, dialysis center and family physician.
- The patient may be brought in for re-assessment with the transplant team if deemed appropriate.
- Once all information is available, the patient's file is reviewed at the weekly transplant team rounds.
- Patients who no longer fulfill the eligibility criteria will be removed from the waitlist.
- Communication with the primary nephrologist regarding this decision is made with a formal letter and may include direct phone conversation.
- The referring nephrologist or a member of the Transplant Team will inform their patient of the transplant team's decision.

1.7 DONOR SELECTION

Kidneys are obtained from two sources, either a living donor, or a deceased donor.

Living Donor

There are several advantages to having a living donor transplant:

Advantages of Living Donor Transplants

- *It provides the greatest chance of a successful transplant outcome*
- *It allows the potential for pre-emptive transplantation*
- *It allows the recipient to avoid a lengthy wait on the deceased donor transplant list*
- *You can plan for the date of the transplant*
- *It helps to alleviate the critical shortage of organs from deceased donors*
- *The National Kidney Paired Donation Program (CBS) makes live donor transplantation feasible for a greater number of individuals (e.g., KPD & NDAD)*

To prepare for a transplant from a living donor, members of the transplant team will:

- Discuss living donor transplantation with the recipient
- Encourage discussion between potential donors and the recipient
- Describe in detail the procedure, implications, risks and benefits to the intended donor
- Take blood samples for ABO, HLA typing, virology and initial cross match to identify the optimal donor match
- Encourage the donor to carefully consider the decision to donate before proceeding and discuss all questions fully
- Perform the evaluation which covers all medical, surgical, social and psychological aspects
- Book the surgery
- Repeat the cross match prior to surgery

If an individual expresses an interest in living organ donation, the person should contact the transplant nurse at Vancouver General Hospital, Transplant Nurse at St. Paul's Hospital or the Transplant Coordinator at BC's Children's Hospital.

If a donor is healthy but not able to directly donate to the transplant candidate of their choice they will be given the option of entering into the Canadian Living Donor Paired Exchange Program (LDPE). In a paired exchange program the chance of finding a matching donor increases if there are more donor recipient-pairs from which to select. The LDPE registry is now active across Canada and the number of donor-recipient pairs is increasing so that the chances of finding a match are reasonable: Refer to CBS website at [LDPE](#). Also See BCT Clinical Guidelines – [Living Donation Kidney](#)

Deceased Donor

The suitable deceased kidney donor:

- Is normally less than 75 years of age
- Has no evidence of irreversible renal dysfunction
- Has no known transmittable disease or malignancy

Limitations in Donor Screening and Testing

Despite the extensive screening and testing that is done on every donor, there are still limitations:

- *There are not screening tests for every transmissible pathogen, and there are risks of both false positive and false negative test results. In addition, there is a period of time when infection(s) is not detectable (i.e. window period).*
- *Risk assessment histories reflect only the knowledge of the person providing the history.*

In situations where there is the potential of disease transmission the kidney may be utilized with the recipient's consent (See Section 3.8 [Exceptional Distribution – Follow up of recipients](#))

1.8 Kidney Organ Offering and Allocation

Blood from potential deceased donors is sent to the Vancouver General Hospital (VGH) Immunology Lab where HLA typing and cross matching with the wait listed patients is performed. Kidneys are offered to transplant programs as per documented BC Transplant (BCT) Standard Operating Procedure (SOP), Organ Offering and Allocation (Renal).

The BCT Organ Donation and Hospital Development (ODHD) Coordinator allocates the kidney with priorities determined by the transplant nephrologist (after consultation with BCT Medical Director of Quality or authorized designate).

NOTE: Pediatric names are automatically first on the Tissue Typing Results list.

Offering Kidneys Out of Province / Out of Country:

If unable to allocate kidneys within BC, then ODHD will inform the on-call transplant nephrologist that there is no appropriate recipient for kidneys within BC and that the kidneys may need to be offered extra-provincially.

If a BC kidney program does not have a suitable recipient, the ODHD Coordinator shall offer the organ out nationally, offering sequentially from the geographically nearest Canadian center to the farthest (i.e., first to Edmonton versus Toronto).

Kidneys may only be offered in Canada to Organ Procurement Organizations registered with Health Canada.

Kidneys may be offered to the US when all applicable Canadian OPO's have declined the offer; and may only be offered through UNOS.

ADDITIONAL RESOURCES

[Kidney, pancreas, and pancreatic islet transplantation](#). D. Landsberg, RJ Shapiro. 2010. BCMJ Vol 52:189-196

[Canadian Society of Transplantation: consensus guidelines on eligibility for kidney transplantation](#). 2005. Knoll et al. CMAJ Vol173: S1-S25.

[Kidney Allocation in Canada: A Canadian Forum](#). Report and Recommendations. CCDT Toronto, Ont. 2006.

[Risk of Disease Transmission from Organ Donors - Patient Information Guide](#)

BCT SOP, Organ Offering and Allocation – Renal [ODHD-ODS.02.005].

2 Transplant

2.1 ADMISSION

It is critical patients on waitlist maintain their contact information current and updated with BC Transplant. When a donor organ becomes available, the transplant candidate is contacted by a member of the BC Transplant Team and travels to the transplant centre as requested. On admission to the transplant centre a medical assessment is performed.

The following tests are performed:

Patient Investigations

Routine investigations performed upon admission include:

- CBC and platelet count
- PTT and INR
- Blood group; crossmatch of 2-4 units packed red cells
- Electrolytes
- Urea, creatinine and uric acid
- Albumin and total protein
- AST, ALT or gamma GT and alkaline phosphatase
- Transplant immunology (10 cc of clotted blood)
- Chest X-ray
- 12-lead electrocardiogram
- MSU for culture and sensitivity (if possible)

If a severe medical problem is identified at this time the patient may be unable to receive the transplant.

Surgery Preparation

Preparations for transplant surgery consist of:

- Dialysis if required
- Surgical preparation
- Notation of last mealtime (nothing by mouth)
- Explanation of procedure to patient; signing of surgical consent form by patient
- Establishment of time of surgery and notification of next-of-kin
- Insertion of IV or saline lock as appropriate
- Administration of prophylactic antibiotics: cefazolin 1 gram IV on call to OR and 1 gram every 12 hours for 3 doses. If allergic to penicillin, administer clindamycin 600 mg IV on call to OR and 600 mg IV every 8 hours for 24 hours

Refer to most current *Renal Transplant Pre-Op Orders*

2.2 TRANSPLANT OPERATION

The renal allograft is placed extra-peritoneally in the right or left iliac fossa (See Figure 2). Vascular anastomosis are between the donor renal vessels and usually the external iliac vessels of the recipient. Urinary reconstruction is almost always via uretero-neocystostomy (donor ureter to recipient bladder), although at times, other types of reconstruction may be chosen. Initial function is enhanced by short cold ischemic times, short re-warm (anastomosis) times, and intravascular volume repletion.

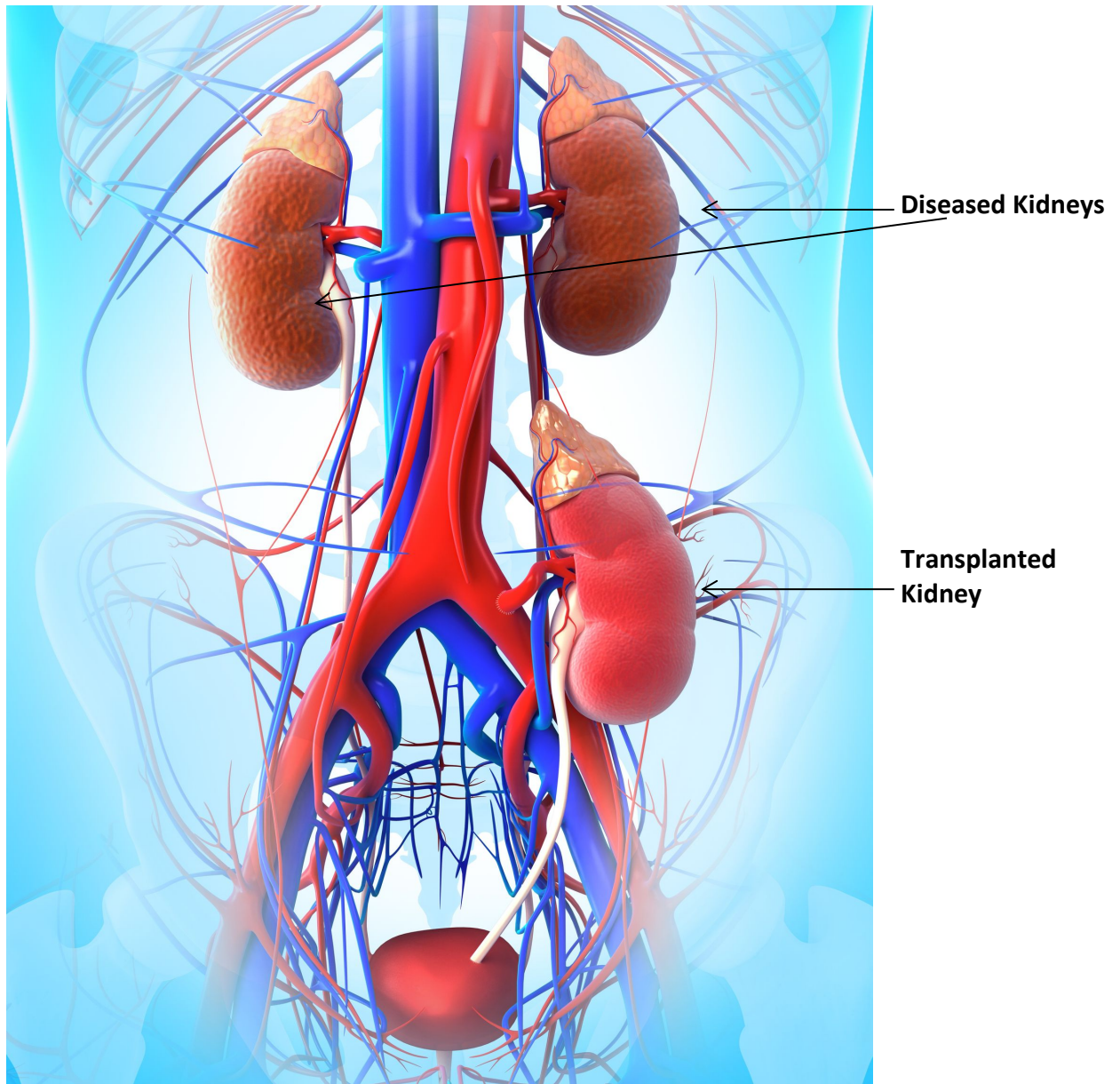


Figure 2. Renal Transplant Anatomy.

2.3 IMMUNOSUPPRESSION

Immunosuppressive therapy is based on the transplant recipient's immunological risk and donor factors.

Immunologic Low Risk

This group consists of first-time transplant recipients who have less than 20% panel-reactive antibodies and no donor specific antibodies, and repeat transplant recipients who have not aggressively rejected a previous transplant (i.e. not within the first year) and who have less than 20% panel-reactive antibodies and no donor specific antibodies.

Low immunologic risk recipients receive initial therapy with an IL-2 receptor blocker, basiliximab, a calcineurin inhibitor (cyclosporine or tacrolimus, mycophenolate mofetil and perioperative steroids). Most low immunologic risk recipients should have a rapid steroid elimination protocol (see Table 1).

Immunologic Intermediate Risk

This group consists of transplant recipients with panel-reactive antibodies between 20% and 80% and no donor specific antibodies.

Intermediate immunologic risk recipients receive quadruple therapy with an IL-2 receptor blocker (basiliximab), a calcineurin inhibitor (tacrolimus or cyclosporine), prednisone, and mycophenolate mofetil.

Immunologic High Risk

This group consists of transplant recipients who have rejected one or more transplants aggressively (i.e. within the first year post transplantation), or any recipients with greater than 80% panel-reactive antibodies.

Transplant candidates receive quadruple therapy consisting of an anti-thymocyte globulin (Thymoglobulin®), a calcineurin inhibitor (cyclosporine or tacrolimus), prednisone, and mycophenolate mofetil.

High Donor Risk (Donors at high risk for delayed graft function)

Early use of calcineurin inhibitors (CNI's) may increase the risk of delayed graft function (DGF) therefore CNI's are avoided in donors known to have predetermined high risk for DGF. Risk factors include donor age greater than 60 years, acute kidney injury and prolonged cold ischemic time.

TABLE 1. Summary of Initial Immunosuppressive Therapy Based on Immunologic Risk Status of Transplant Candidate

(Refer to Clinical Guidelines for Transplant Medications for more specific information) May 2021

Immunological Low Risk Transplant Candidate	Immunological Intermediate/Moderate Risk Transplant Candidate	Immunological High Risk Transplant Candidate	High Donor Risk (DCD/ECD) (Risk for DGF-delayed graft function)
Intra-Operative Immunosuppression			
Basiliximab 20 mg IV day 0 of transplant, intra-operatively.	Basiliximab 20 mg IV on day 0 of transplant, intra-operatively.	Anti- thymocyte globulin (rATG): 1.5 mg/kg intra-operatively	Anti- thymocyte globulin (rATG): 1mg/kg intra-operatively
Methylprednisolone 125 mg IV intra-operatively	Methylprednisolone 125 mg IV intra-operatively	Methylprednisolone 500 mg IV POD 0 with first dose of rATG	Methylprednisolone 500 mg IV POD 0 with first dose of rATG
		Start immediate release tacrolimus POD 0 as soon as patient tolerating PO	Delay starting tacrolimus if DGF
Post-Operative Immunosuppression			
Basiliximab 20 mg IV on day 4 of transplant	Basiliximab 20 mg IV on day 4 of transplant	Anti- thymocyte globulin (rATG) 1.5 mg/kg x 3 days (Max. 6 mg/kg total dose). To be reassessed daily	Anti- thymocyte globulin (rATG) 1 mg/kg (Max. 3 to 4.5 mg/kg total dose depending on clinical status). To be reassessed daily.
Methylprednisolone 125 mg IV POD 1, then no further steroids.	Methylprednisolone 125 mg POD 1, then prednisone 60 mg POD 2, taper by 10 mg daily until 20 mg daily. Taper prednisone as per primary transplant centre	Methylprednisolone 125 mg POD 1, then prednisone 60 mg POD 2, taper by 10 mg daily until 20 mg daily. Taper prednisone as per primary transplant centre	Methylprednisolone 125 mg POD 1, then prednisolone 60 mg POD 2, taper by 10 mg daily until 20 mg daily. NOTE: Stop steroids if patient longer with DGF risk and low immunologic risk
When patient tolerating PO, begin tacrolimus IMMEDIATE release 0.075 mg/kg/dose PO bid. Adjust for a trough level of 10 to 12 mcg/mL (TMS assay). If not able to take PO tacrolimus IV (1/4 of PO dose is given)	When patient tolerating PO, begin tacrolimus IMMEDIATE release 0.075 mg/kg/dose PO bid. Adjust for a trough level of 10 to 12 mcg/mL (TMS assay). If not able to take PO tacrolimus IV (1/4 of PO dose is given)	When patient tolerating PO, begin tacrolimus IMMEDIATE release 0.075 mg/kg/dose PO bid. Adjust for a trough level of 10 to 12 mcg/mL (TMS assay). If not able to take PO tacrolimus IV (1/4 of PO dose is given)	When renal function established, start tacrolimus IMMEDIATE release 0.075 mg/kg/dose PO bid. Adjust for a trough level of 10 to 12 mcg/mL(TMS assay)
Mycophenolate mofetil 1 gram PO bid as soon as patient can take PO medications			

2.4 ROUTINE POST-OPERATIVE REGIMEN

During the early post-op period, the patient remains under close observation. The routine post-operative regimen involves the following investigations and treatments:

Clinical Examination

A clinical examination, urine output, blood pressure and weight are monitored daily. Daily lab investigations include: serum creatinine (SCr), and calcineurin inhibitor (CNI) blood concentrations with results recorded in the patient's chart.

Patients have central venal pressure (CVP) monitoring in early post-operative transplant period.

Prophylactic Antibiotic Treatment

Prophylactic antibiotic treatment is continued for 24 to 36 hours following transplantation.

Nutrition

Diet is increased as tolerated when intestinal activity is re-established, although sips of water may be permitted before that. The patient starts with a clear fluid diet, then proceeds to full fluids and then advances to a solid diet as quickly as can be tolerated. Total fluid intake must be balanced daily against the volume status of the patient.

Foley Catheter

During the transplant operation, an indwelling Foley catheter is inserted into all patients. The Foley catheter ensures the bladder is well drained and reduces strain on the ureter anastomosis.

Initially, the urine output is recorded hourly. The catheter normally stays in place for a minimum of two to five days. A retrograde cystogram may be done prior to removing the Foley catheter.

Peritoneal Dialysis (PD) Catheter

Patients on peritoneal dialysis (PD) must be drained before going to the operating room for transplant. As long as the peritoneal cavity is not entered during surgery, peritoneal dialysis may be performed post-transplant as needed. The catheter can be removed as early as one month after transplant if the patient is stable.

Wound Care

The patient's incision is managed according to standard hospital protocols.

Refer to most current *Renal Transplant Post-Op Orders*

3 POST-TRANSPLANT

3.1 COMPLICATIONS IN EARLY POST-OPERATIVE PHASE

Major Complications which can occur in the early post-operative phase include:

- Delayed graft function (DGF)
- Infection
- Graft rejection

Delayed Graft Function

Poor initial graft function occurs in less than 5% of living donor recipients and less than 20% of deceased donor recipients.

The patient is normally oliguric, although non-oliguric renal dysfunction may occur. When the transplanted kidney is not functioning it is critical to exclude arterial or venous occlusion and urinary obstruction or leak. This is determined by an urgent ultrasound with Doppler to assess kidney flow. Patients with surgical problems may need urgent reoperation. The overwhelming majority of kidney grafts with poor function may simply have a delay in graft function. Dialysis will be instituted and fluid and dietary restrictions are commenced as appropriate. All medications requiring dosage adjustments for renal failure are reviewed.

Infection

Infection remains an important cause of morbidity and mortality following transplantation, although the use of prophylactic antibiotic therapy at the time of surgery has markedly decreased these risks. Infection occurs in up to 30% of renal transplant recipients during the first three months after transplant. Early diagnosis and appropriate treatment are essential.

Bacterial infection:

Most common during the first four weeks post-transplant. Infection may occur at the wound site, in the urinary tract, or in the lung. If inadequately treated, local infection may rapidly progress to systemic sepsis, particularly in diabetic patients.

Viral infection:

Usually seen between 4 to 26 weeks after transplant, particularly in individuals treated with anti-thymocyte globulin. The principal viral infections are:

- **Herpes simplex (HSV) stomatitis:** common in patients with prior infection and responds rapidly to acyclovir or valacyclovir therapy.
- **Cytomegalovirus (CMV) infection:** occurs predominantly in individuals harboring the latent virus, or in those receiving a graft from a sero-positive donor. The clinical presentation may range from fever and leucopenia to a severe life-threatening illness with pneumonitis, hepatitis, marrow aplasia and esophagastroenteritis. Patients at high risk for CMV disease may receive either prophylactic or pre-emptive treatment with oral valganciclovir or ganciclovir IV. CMV disease is treated with ganciclovir IV or oral valganciclovir. Patients are monitored for CMV using the CMV-PCR test. (Refer to Clinical

- **Epstein-Barr virus infection:** may occur in a similar timeframe to CMV. This infection may occur in sero-negative recipients who receive a kidney from a sero-positive donor. With primary EBV infection there is a spectrum of clinical disease ranging from sore throat and fever to post transplant lymphoproliferative disease (LPD).
- **BK Polyoma Virus (BKV):** Asymptomatic viruria with BKV occurs in approximately 30% of kidney transplant recipients. Viruria occurs between 2 weeks and 2 years after transplantation and indicates viral replication within the kidney or urinary tract with subsequent shedding of virus and uroepithelial cells in the urine. Viruria precedes viremia which precedes kidney invasion. Very rarely BKV infection may present with ureteral obstruction after ureteral ulceration and stenosis due to smooth muscle proliferation at the ureteric anastomosis. Less than half of the patients who develop BK viruria develop BK viremia. Many patients with BK viremia go on to develop BK infection in the transplanted kidney. We monitor patients for viremia rather than viruria as this is the most cost effective strategy.

(BK Management Guideline below)

Fungal infection: occurs in a small proportion of patients, particularly those at risk because of co-existing diabetes mellitus, previous immunosuppression, or prolonged instrumentation or drainage. Oral candidiasis is the most common fungal disease in the early post-transplant period. Oral candidiasis has been decreased by the routine use of nystatin. More severe fungal infections are rare but transplant recipients are at some risk for cryptococcus, mucormycosis, aspergillosis and nocardia infections.

Graft Rejection

Graft rejection episodes occur in less than 20% of low risk transplant recipients within the first 26 weeks after transplantation. It is important to remember most rejection episodes are reversible. There are usually no symptoms of rejection. The diagnosis of rejection is usually made by a rise in serum creatinine (SCr). Other causes for a rise in serum creatinine including increased calcineurin inhibitor blood concentrations, volume factors, and surgical factors must be ruled out. The diagnosis of rejection is confirmed with kidney biopsy.

There are four main types of rejection experienced by renal transplant recipients:

- Hyperacute
- Accelerated
- Acute
- Chronic

3.2 MANAGEMENT OF RENAL DYSFUNCTION

Figure 3 outlines the stages in managing acute renal dysfunction.

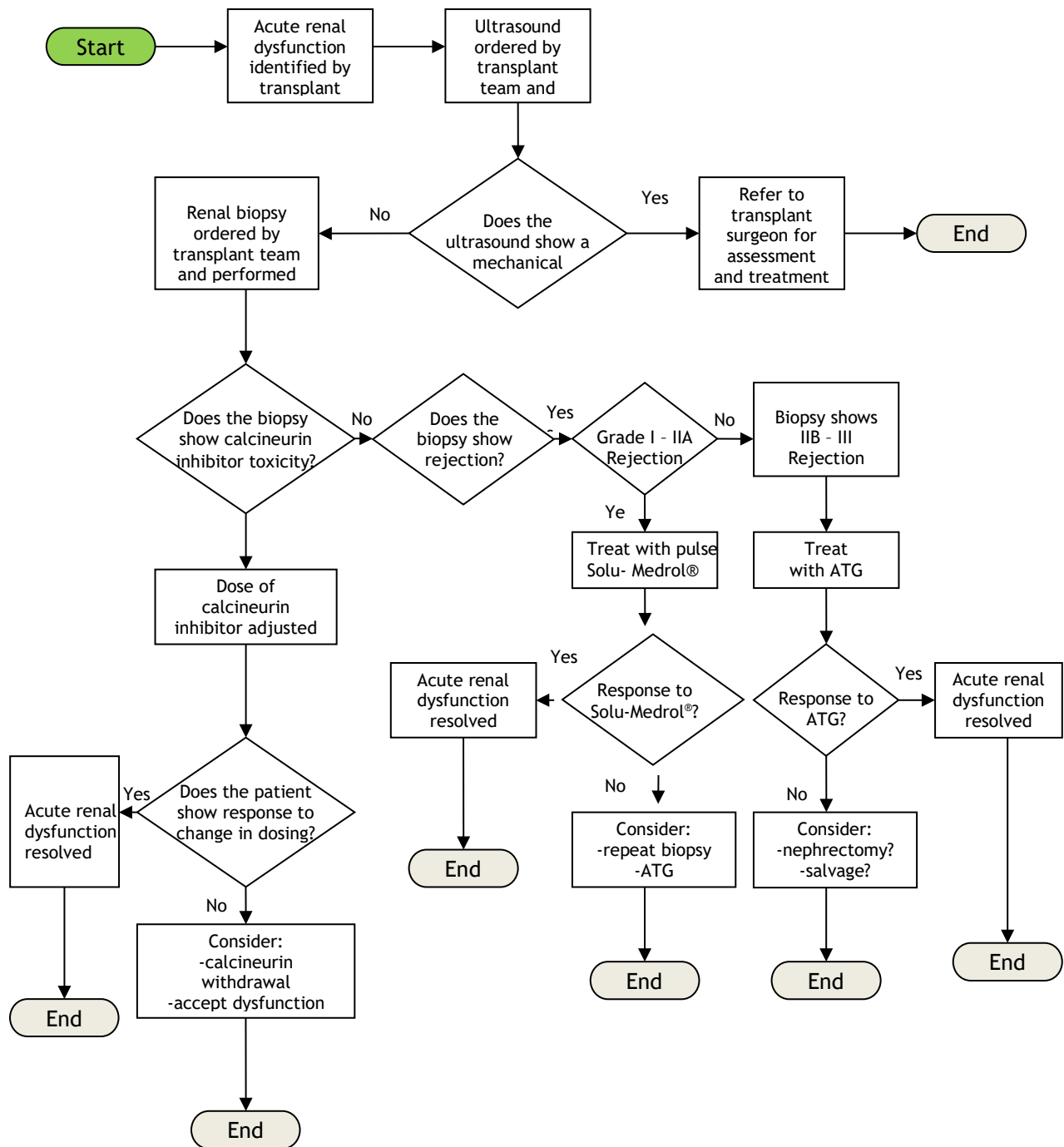


Figure 3. Management of Acute Renal Dysfunction Post-Treatment

3.3 TYPES OF REJECTION

There has been extensive work done to clarify types of transplant rejection. The best reference is [Banff 97 working classification of renal allograft pathology](#) (*Kidney International*, Vol. 55: 1999; 713-723).

Types of Rejection and Immune Response			
	Rejection	Time	Immune Response
1	Hyperacute	Immediate	B-cell
2	Accelerated	2 to 5 days	B-cell
3	Acute	1 week to 3 months	T cells
4	Chronic	3 months to years	B and T cells

1. Hyperacute Rejection

Hyperacute rejection may occur when the transplant recipient possesses pre-formed antibodies to antigens on the donor kidney. It occurs within minutes to hours after transplantation and results in irreversible damage. However, with current cross-matching techniques, hyperacute rejection is very rare.

2. Accelerated Rejection

Accelerated rejection results when the transplant recipient possesses pre-existing antibodies. It occurs within the first week following surgery. It is usually due to recipient's antibodies attacking the donor kidney. These antibodies were likely present prior to the transplant but below the detectable antibody level.

3. Acute Rejection

Acute rejection is most commonly seen one week to three months after the transplant. Patients may experience more than one episode before achieving stable graft function. It is primarily a cell-mediated response. It is associated with an increase in serum creatinine. Other symptoms are rare but in some situations may include reduced urine output, fever, a swollen and tender graft, and edema of the lower extremity on the side of the transplant.

Suspected acute rejection episodes should be confirmed with a biopsy (See [section 3.4](#)).

Episodes of acute rejection may be discussed with the primary transplant centre and management is planned accordingly.

Initial therapy for acute rejection is intravenous methylprednisolone. Administer methylprednisolone (500 mg IV daily for 3 days) as soon as rejection is diagnosed. If the patient responds, on day 4 the patient is placed on oral prednisone which is tapered quickly back down to a baseline of 0.3 mg/kg per day.

Patients who do not respond are termed steroid resistant. These patients may require more aggressive therapy with anti-thymocyte globulin. These patients should be discussed with the primary transplant centre and may warrant a repeat biopsy. Approximately 10% of acute rejection episodes are antibody mediated rather than cell mediated.

4. Antibody Mediated Rejection (AMR)

The diagnosis of antibody mediated rejection (AMR) is based on histology showing capillary involvement, C4d deposition in peritubular capillaries and demonstration of circulating donor specific antibodies (DSA). Treatment usually includes Therapeutic Plasma Exchange (TPE), Intravenous Immunoglobulin (IVIg) and rituximab. The AMR Treatment Protocol outlined in [Appendix VII](#).

5. Chronic Allograft Nephropathy (Chronic Rejection)

Chronic allograft nephropathy usually occurs late, after months or years of stable renal function.

3.4 Renal Biopsy

All suspected acute kidney rejection episodes should be confirmed with a transplant biopsy.

Biopsies should also be performed for the long-term transplant patient who experiences a chronic elevation in creatinine and/or the onset of persistent proteinuria. This will allow the diagnosis of chronic allograft nephropathy/calcineurin inhibitor (CNI) nephrotoxicity and *de novo* or recurrent glomerulonephritis.

Procedure

All biopsies are performed under ultrasound guidance. The ultrasound is important prior to the biopsy to rule out obstruction or an alternate reason for the elevated creatinine. Biopsies are usually performed by the radiologist. Outpatients are usually followed in a day care setting and discharged several hours post biopsy if stable.

Normal International normalized ratio (INR), prothrombin Time (PTT) and platelet counts are required prior to biopsy. Patients taking anticoagulants including ASA and Plavix® need to have these drugs discontinued for a period of 5-7 days and need to have their INR and PTT corrected prior to undergoing a biopsy.

Patients should be monitored for signs and symptoms of bleeding for four hours post biopsy. Signs and symptoms of bleeding include:

- Decrease in blood pressure or increase in pulse rate
- Obvious bleeding at the biopsy site
- Severe pain at the biopsy site or in the flank
- Gross hematuria

3.5 Viral Complications

Cytomegalovirus (CMV)

Cytomegalovirus (CMV) is the most common viral pathogen affecting solid organ transplant recipients. CMV infection usually develops within the first four months post-transplant. The clinical spectrum of CMV disease is wide ranging from a low grade febrile illness to life threatening multi-system infection.

CMV seronegative solid organ transplant patients who have a primary infection have the greatest risk of developing severe CMV disease. Transmission usually occurs through the donor organ, unscreened blood products or intimate contact with a viral shedder. Reactivation of a latent CMV infection or superinfection caused by a donor virus in a CMV sero-positive recipient is less likely to cause severe disease.

The management of CMV infection is stratified according to risk profiles of a given patient population. There are three different therapeutic strategies used in the management of CMV disease and infection:

- CMV prophylaxis
- CMV pre-emptive treatment
- CMV disease treatment

Prophylaxis is begun in the absence of detectable virus or disease and is aimed at prevention of CMV infection or reactivation in high-risk patients. In pre-emptive strategies, treatment is started in the absence of disease symptoms but in the presence of detectable virus in the blood.

(Refer to [Kidney Disease Improving Global Outcomes \(KDIGO\)](#), *American Journal of Transplantation*. 2009: Supplement 3, Vol. 9; S46-8).

(Refer to Clinical Guidelines for [Transplant Medications](#), for more specific information on CMV prophylaxis and treatment regimen and ganciclovir and valganciclovir dosage).

BK Polyoma Virus (BKV)

Polyoma virus (type BK) is an important cause of kidney allograft dysfunction. Polyomaviruses, a subfamily of the *Papovaviridae*, includes two strains known to cause disease in humans: BK virus and JC virus. BK Infection occurs in early childhood. Approximately 50% of children under the age of four and 70% to 80% of adults will have antibody to these viruses indicating prior exposure. Transmission is by respiratory secretions. Viremia during primary infection probably leads to systemic seeding and the development of latent infection. The kidney is the main site of latency in healthy people.

The most commonly reported site of BKV infection and disease is the kidney and urinary tract. BKV has been associated with transient cystitis in immunocompetent children, glomerulonephritis in immunocompromised children and adults, hemorrhagic cystitis in bone marrow transplant recipients and ureteral stenosis and interstitial nephritis (BKV virus nephropathy (BKN)) in kidney transplant recipients.

Asymptomatic viruria with BKV occurs in approximately 30% of kidney transplant recipients. Viruria occurs between 2 and 70 weeks after transplantation and indicates viral replication within the kidney or urinary tract with subsequent shedding of virus and uroepithelial cells in the urine. Very rarely BKV infection may present with ureteral obstruction after ureteral ulceration and stenosis due to smooth muscle proliferation at the ureteric anastomosis.

Less than half of the patients who develop BK viruria develop BK viremia. Many patients with BK viremia go on to develop BK infection in the transplanted kidney.

BK infection in the transplanted kidney, termed BK nephropathy (BKN,) is increasingly recognized as an important cause of graft dysfunction with an incidence of 2 to 5%. BKN is an interstitial nephritis that typically occurs within the first post-transplant year although the time of onset is variable and cases have now been reported after five years of transplantation. There is a progressive decline in allograft function without systemic symptoms of infection.

The mechanisms by which BKV causes interstitial nephritis are unknown. Because BKV is ubiquitous, most cases of BKN occur in patients who were seropositive at the time of transplantation. It has been suggested that seronegative patients who receive an allograft from a seropositive donor may be at increased risk, but this is uncertain.

The increased incidence of BKN in recent years has led to the hypothesis that more potent immunosuppression may potentiate polyoma virus infection (possibly by the outgrowth of mutant strains). Inconsistent associations with tacrolimus and mycophenolate mofetil have been reported. Recently, the number of steroid pulses given for the treatment of acute rejection has been associated with an increased risk of BKN. However, it is probable that the potency of the immunosuppressive regimen rather than the use of any specific agent is the most important factor in the pathogenesis of BKN.

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 immunocompromised 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 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/mL¹.
 - 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 1 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 not 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 therapy² 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 ± 14 mcg/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.

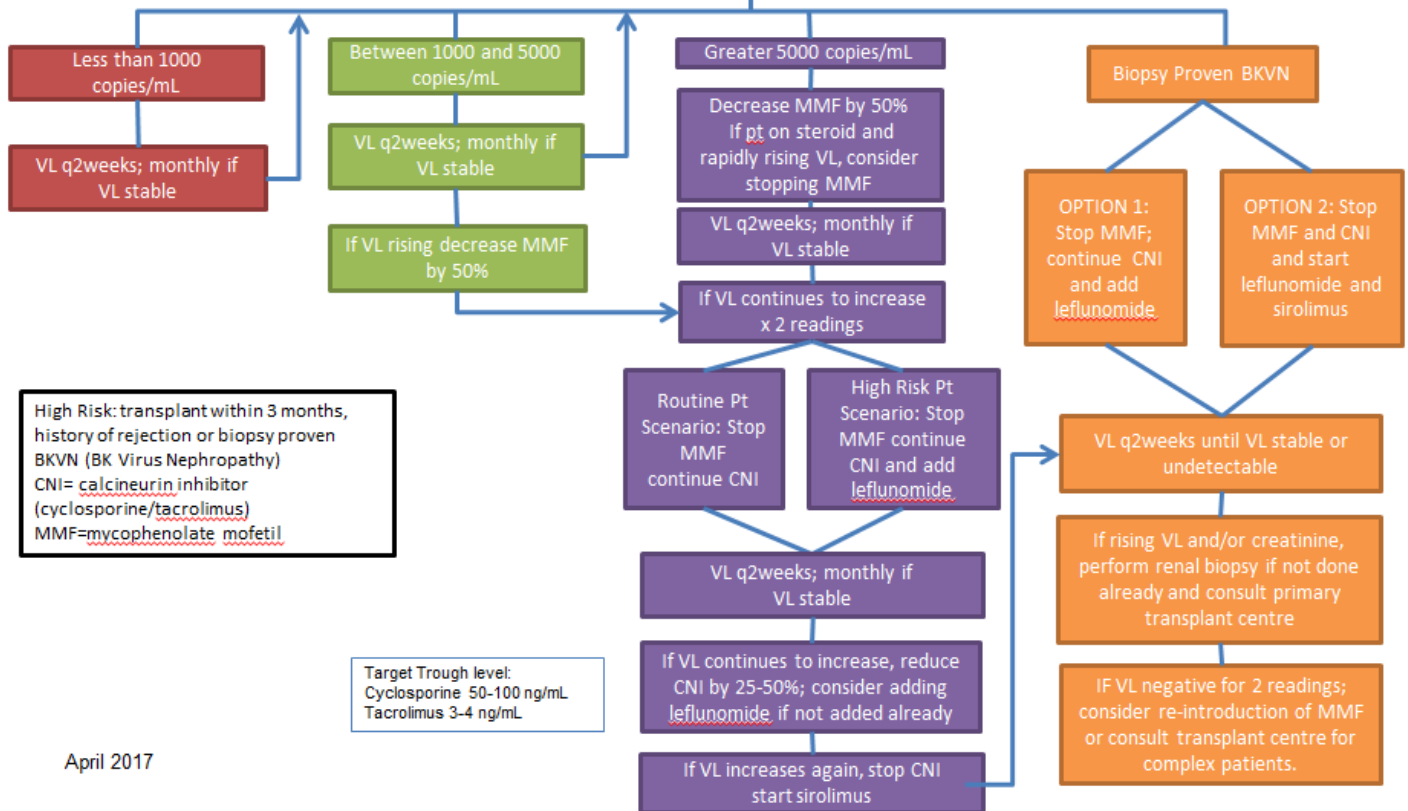
BK Viral Load (VL) Monitoring

BK VL q2weeks for 16 weeks post Tx; then monthly till end of 2 years

OR

BK VL for unexplained rise in serum creatinine or renal biopsy

For first positive BK VL, repeat in 1 week to verify result and establish that it is NOT rising rapidly



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:

Diagnosis of BKN:

With this preventive strategy overt BKN is becoming more uncommon but late disease may occur. Late patients may be diagnosed late because they are no longer being screened for BK viremia. Renal biopsy is the gold standard for the diagnosis of BKN. The histological findings are well described and validated. However many of the findings are non-specific and the interstitial inflammation found in BKN must be differentiated from that of acute rejection. Immunohistochemistry (Staining for SV40 antigen) or electron microscopy can confirm BK virus infection.

Treatment of Polyomavirus BK

There is no antiviral treatment with proven benefit for BKN. Use of the lowest effective dose of immunosuppression may prevent development of disease. Early diagnosis and intervention may also be beneficial. Although differentiating BKN from acute rejection may be difficult, coexistent acute rejection should be treated with pulse steroids. With isolated BKN, the **mainstay of treatment is to reduce immunosuppression**. Both cidofovir and leflunomide have been suggested as treatment options but there should be restricted to salvage situations as they have significant toxicities.

(Refer to [Kidney Disease Improving Global Outcomes \(KDIGO\)](#), *American Journal of Transplantation*. 2009; Supplement 3, Vol. 9; S44-6).

Hepatitis B

Hepatitis Testing:		Interpretation
HBsAg	Hepatitis surface antigen	HBV infection
HBcAB	Antibody to hepatitis B core antigen	Exposure to HBV infection may be active or inactive.
HBsAb	Antibody to hepatitis B Surface antigen	Immunity to HBV (vaccine induced or a result of prior infection)
HBV DNA	Hepatitis B viral load	Active replication of HBV
HBeAg	Hepatitis B e antigen	Marker of replication and infectivity
HBeAb	Antibody to Hepatitis B e antigen	Suggests viral clearing and recovery

Patients for whom therapy is indicated:

All patients with HBV who receive immunosuppressive therapy are at higher risk for developing exacerbation of hepatitis after transplant. This may also occur in non-replicating patients (HBsAg positive but DNA negative) and even in those who are only HbcAB positive thus it is important to start antiviral therapy for hepatitis B before initiating immunosuppressive therapy or at the time of initiation. Antiviral therapy should be maintained throughout the course of treatment for previously replicating patients. Anti-viral therapy is rarely discontinued.

Monitoring Therapy and Assessing Outcomes:

Patients are followed by the GI/hepatology team post-transplant with follow up bloodwork every three to six months until HBV DNA is undetectable, thereafter once a year for review. The goal of anti-HBV therapy is to decrease and / or prevent progression of liver disease and development of hepatocellular carcinoma.

- HBV DNA, ALT, CBC levels every 12 weeks and HbeAg or HbcAB levels every 12 months.
- Abdominal Ultrasound every 6 months

References

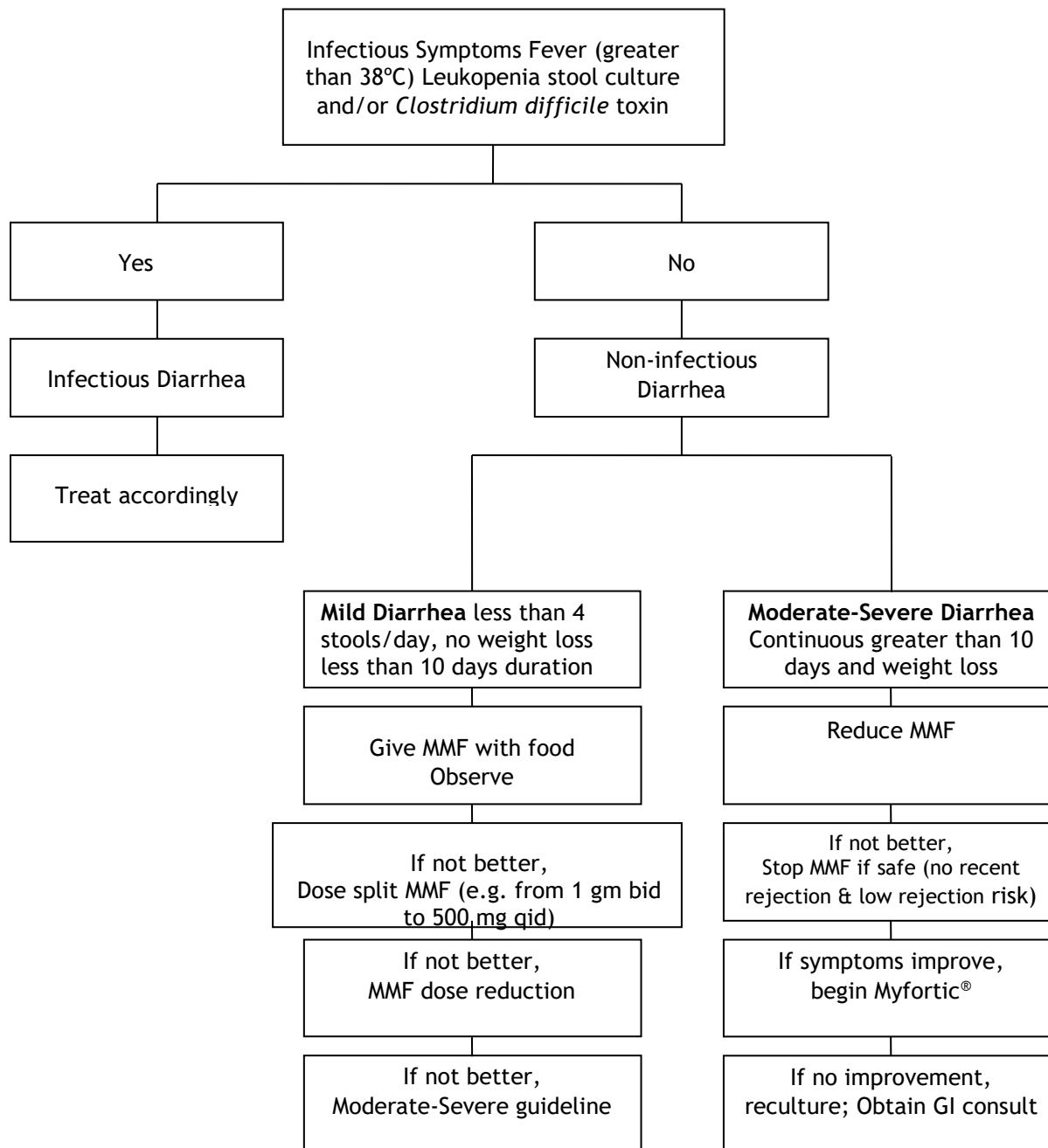
[NIH Consensus Development: Management of Hepatitis B](#), Sorrell et al., *Annals of Internal Medicine*, 150 (2) 104-110.

[Kidney Disease Improving Global Outcomes \(KDIGO\)](#), *American Journal of Transplantation*. 2009: Supplement 3, Vol. 9; S53-7).

3.6 DIARRHEA

Diarrhea is a frequent problem in post-transplant patients. One must make a distinction between medication induced and infectious diarrhea. Refer to Figure 4.

Figure 4. **Treatment of Post-Transplant Diarrhea**



References

- Davies NM et al. [Gastrointestinal side effects of mycophenolic acid in renal transplant patients: a reappraisal](#). *Nephrol Dial Transplant*. 2007; 22; 2440-2448.
- Maes B et al. [Severe diarrhea in renal transplant patients: results of the DIDACT study](#). *Am J Transplant*. 2006;6; 1466-1472.

3.7 LEUKOPENIA

The following is how leukopenia is managed in post-renal transplant recipients.

Low white blood cell count (WBC) is seen frequently post renal transplant. Most commonly it is related to a medication. Mycophenolate, azathioprine, and valganciclovir are the most commonly implicated medications. Cotrimoxazole and many other medications are also associated with low WBC.

If patient has markedly low WBC (neutrophil count less than $0.5 \times 10^9/L$) and is febrile/unwell, they should be admitted to hospital, placed on protective isolation plus broad spectrum antibiotics plus G-CSF. Offending drugs can be held. If it is believed the low WBC is secondary to CMV, continue ganciclovir therapy or valganciclovir and support with G-CSF. Patients who remain well and afebrile can be managed as outpatients.

Approach to Low WBC. Patients that have $WBC < 3.0 \times 10^9/L$ need to be further evaluated for their low count. In the absence of infection (no system signs of infection, afebrile, no CMV viral load) a medication review is necessary.

1. Have any new medications been started?
2. Is the patient taking the correct dose of medications?
3. Has valganciclovir been dosed adjusted for renal function?

If the patient is on azathioprine, you must ensure that they have not been started on allopurinol. (Patients on azathioprine that require allopurinol for control of gout require a reduction of their azathioprine dose to $\frac{1}{4}$ or $\frac{1}{2}$ of their prior dose, with surveillance of their WBC).

Most patients will be on several potential medications that could cause their leukopenia. In the absence of identifiable cause, the asymptomatic patient should have their Mycophenolate dose reduced by 50%. Continue following weekly CBC and differential. If the counts do not improve, the Mycophenolate can be held. Reintroduction of mycophenolate should wait until the counts are recovering. Once the WBC is $4.0 \times 10^9/L$ or greater, a step wise reintroduction of mycophenolate can begin.

If altering the dose of mycophenolate does not work and the patient is on other medications that can cause leukopenia the potential offending medications should be stopped. (If a patient is being treated for CMV, they must continue their therapy with ganciclovir/valganciclovir and supported with G-CSF is necessary). Patients that are on CMV prophylaxis can have their valganciclovir stopped, but need ongoing surveillance of their CMV viral load. If elimination of ganciclovir/valganciclovir does not result in normalization of WBC, stop the cotrimoxazole. Patients that do not respond to these interventions should be seen in consultation by hematology.

3.8 Exceptional Distribution – Follow-up of Recipients

Human cells, tissues and organs that are to be used in transplantation are regulated under Health Canada's [Safety of Human Cells, Tissues and Organs for Transplantation Regulations](#) (CTO Regulations), Dec 2007. This includes kidneys both from deceased and living kidney donors.

The purpose of the CTO Regulations is to minimize the potential health risks to Canadian recipients of human CTO by addressing the safety in the processing and handling of these products. Source establishments must determine that donors are not unsuitable to donate on the basis of the contraindications or exclusion criteria set out in the Regulations.

However, it is recognized that in exceptional circumstances and compassionate reasons, a kidney may be transplanted even when there may be a contraindication during donor assessment (e.g., incomplete donor screening). This decision is made when the transplant team along with the recipient believes that the benefit of receiving this transplant exceeds the risk of illness from transmission of disease from the donor. The process is documented on an [Exceptional Distribution Form](#) by the BCT ODHD Organ Donation Coordinator. The transplanting physician must authorize the exceptional distribution including obtaining informed consent of the recipient. Copies of the exceptional distribution form are to be included in the Recipient chart.

It is important that in all cases, appropriate follow-up of recipients is performed by the post-transplant medical care team. Each exceptional distribution is to be reviewed and assessed by the team for any follow-up treatment and diagnosis.

Risk for Viral Mediated Disease Transmission

In Exceptional Distribution cases involving risk for viral mediated disease transmission, the following will be sent from BCT Quality Assurance to the transplant hospital or outpatient location:

1. [Copy of the Exceptional Distribution Form](#) (Appendix IV)
2. [Reference – Recommended Follow-up Testing for Recipients Transplanted under Risk for Viral Mediated Disease Transmission](#) (Appendix V)

The post-transplant nurse will ensure the above documents are reviewed by the post-transplant medical care team and the recommended follow-up is performed at the required intervals.

3.9 Ambulatory Care Phase

For an uncomplicated renal transplant the patient normally remains in hospital for four days. Once stable, the patient is discharged for follow-up in the transplant outpatient clinic.

RECOMMENDED FREQUENCY OF FOLLOW-UP AT TRANSPLANT OUTPATIENT CLINIC	
Time, Post-Transplant (months)	Frequency of Routine Outpatient Visits
0 to 1	Twice every week
1 to 2	Once every week
2 to 3	Once every 2 weeks
3 to 6	Once every 3 weeks
6 to 12	Once every 4 weeks
Greater than 12	Patient should have mini bloodwork done every 4 to 6 weeks between clinic visits Clinic visit once every 12 to 16 weeks

This regimen assumes that the patient is clinically stable. The frequency of follow-up may be modified at any time at the discretion of the physician.

Follow-up Process

Patients are followed at the transplant center outpatient clinic for approximately the first 12 weeks post-transplant until they are clinically stable and at a lower risk of rejection. At this point, out-of-town patients are referred to the appropriate regional centre to be followed up by the regional transplant clinic staff.

The transplant team discusses medical problems and agrees on an approach. The status and progress of all patients are reviewed at regular intervals in the transplant centers and discussed with the medical director and staff of the regional transplant clinics as required. This collaborative arrangement lets patients receive most of their clinical care within their own region. Return to the primary transplant center can be minimized once patients are clinically stable. Graft rejection episodes or other serious complications may require return to the primary transplant centre for evaluation and management.

Ongoing follow-up is carried out in the BC Regional Transplant Clinics. The Regional Transplant Clinics are encouraged to discuss complicated management decisions with the primary transplant centre.

3.10 STANDING LAB ORDERS

Routine Tests (Pre-clinic)

Blood work: Prior to each clinic visit, patients should have the following routine blood work done:

- CBC (Hgb, platelets, WBC, differential)
- K, Na, Cl, CO₂, Ca, PO₄
- Glucose (fasting)
- Creatinine, urea
- Total and direct bilirubin
- Liver enzymes – alkaline phosphatase, ALT, AST
- Albumin

Cyclosporine: Cyclosporine blood concentrations are required for patients on cyclosporine. Blood concentrations taken two hours post cyclosporine dose (C₂) are preferred over trough levels.

Tacrolimus: Trough levels are required for patients on tacrolimus.

Sirolimus: Trough levels are required for patients on sirolimus.

Fasting Blood Sugar and HgA1C: All patients should have fasting blood sugars done with all of their bloodwork in the first 6 weeks post-transplant and then at least every 3 months. All diabetic patients should have an HgA1C done every three months. HBA1C testing is not recommended for screening in non-diabetics.

Lipid studies: All patients should have lipid studies (total cholesterol, LDL, HDL and triglycerides) done every 6 months post-transplant.

Urine tests: Prior to each clinic visit patients should have a urinalysis and urine albumin creatinine ratio (ACR). ACR replaces the 24 hour urine. If the values are abnormal, then follow-up tests may be done at more frequent intervals.

Virology tests:

- CMV viremia testing (Refer to Clinical Guidelines for Transplant Medications for more specific information on CMV prophylaxis and treatment regimen and CMV PCR testing)
- BK polyoma: viral testing for all patients (see section 3.5 [Viral Complications](#), BK Polyoma Virus)

Mini Blood Work

The following blood work is done when the patient requires follow-up and review between clinic visits (additional tests are ordered by the physician on an individual basis):

- CBC (Hgb, WBC, platelets, differential)
- K, Na, Cl, CO₂
- Urea, creatinine
- Drug levels

3.11 LONG-TERM IMMUNOSUPPRESSION REGIMEN

Patients remain on immunosuppression for the life of their transplanted kidney. The goal is to minimize immunosuppressive side effects and complications balanced with providing enough immunosuppression to prevent transplant rejection. Generally immunosuppressive dose reductions may begin after the third month post-transplant.

(Refer to Clinical Guidelines for [Transplant Medications](#) for more specific information)

3.12 LONG-TERM ADDITIONAL MEDICATIONS

Adult Patients:

Patients are prescribed prophylactic trimethoprim-sulfamethoxazole (Cotrimoxazole, Septra) for Pneumocystis Pneumonia while receiving high dose immunosuppression.

- Cotrimoxazole single strength (Septra) 1 tablet PO daily or Cotrimoxazole double strength (Septra DS) 1 tablet PO on Mondays, Wednesdays and Fridays.
- Cotrimoxazole (or alternate PJP/PCP therapy) should be administered for at least one year post transplant. For patients tolerating cotrimoxazole, consider lifelong therapy.
- Re-introduce cotrimoxazole (or alternate PJP prophylaxis) anytime patients are receiving increased immunosuppression or undergoing therapy for rejection.
- If patients are allergic to cotrimoxazole, consult the primary transplant centre for alternative prophylaxis.
- Alternatives include:
 - Dapsone 100 mg PO three times a week.
- If patient is allergic to dapsone, alternative is:
 - pentamidine 300 mg inhalation administered through aerosolized nebulizer every 4 weeks for 1 year post transplant. Re-evaluate possible restarting of cotrimoxazole.

Pediatric Patients: (Consult BCCH Transplant Program for PJP therapy)

Patients are prescribed prophylactic trimethoprim-sulfamethoxazole (Cotrimoxazole, Septra®) for Pneumocystis Pneumonia while receiving high dose immunosuppression. Administer 5 mg/kg/day trimethoprim component ONCE daily or divided bid on 3 consecutive days per week OR on Monday, Wednesday and Friday. Maximum 2 tablets per day or 20 mL per day.

Cotrimoxazole should be administered for at least one year post transplant.

Restart cotrimoxazole anytime patients are receiving increased immunosuppression or undergoing therapy for rejection.

If patients are allergic to cotrimoxazole:

- dapsone 2 mg/kg/day PO three times a week. maximum 100 mg per dose.

If patient is allergic to dapsone:

- Pentamidine pediatric dose: age less than 5 years: 8 mg/kg/dose via nebulizer every 4 weeks. Maximum 150 mg per dose.
- Age greater than 5 years: 300 mg via nebulizer every 4 weeks.

Cotrimoxazole (TMP-SMX) Desensitization Protocol for Outpatient Use (Vancouver General Hospital Protocol 2013)

Indication:

Gastrointestinal symptoms or rash secondary to TMP-SMX

Basic Solution:

Dilute 1 mL of pediatric suspension (contains 8 mg trimethoprim and 40 mg sulfamethoxazole) with 9 mL of normal saline. M: 130 mL

Day # (Date)	Septra (mL Basic Solution)	Sulfamethoxazole (mg)
#1	0.25	1
#2	0.5	2
#3	1	4
#4	2	8
#5	5	20
#6	10	40
#7	15	60
#8	20	80
#9	25	100
#10	50	200
#11	1 regular tablet (single strength) daily	400

Anti-hypertensive therapy:

Hypertension is a common post-transplant problem. Rational anti-hypertensive therapy includes calcium channel blockers, beta blockers, or angiotensin converting enzyme (ACE) inhibitors as first line agents. Although calcium channel blockers and ACE inhibitors are expensive, they are effective and may have a nephro-protective effect. ACE inhibitors and angiotensin II receptor blockers (ARB's) should not be used early post-transplant period as they may confound rising serum creatinine. Serum creatinine and potassium levels should be checked at weeks one and two post commencement of an ACE inhibitors or ARB's.

There is a known drug interaction between diltiazem and calcineurin inhibitors. Transplant centres may wish to exploit this interaction and place patients on diltiazem to allow lower doses of tacrolimus or cyclosporine to achieve the same therapeutic levels. Dosage is usually diltiazem CD 180 mg PO once daily. This drug should not be used if there is a documented allergy or if the patient's cardiac status precludes it (e.g. hypotensive with poor cardiac outlook, congestive heart failure with an ejection fraction less than 35%).

3.13 TREATMENT OF A FAILED TRANSPLANT KIDNEY

There are no evidence-based guidelines on how failed transplanted kidneys should be managed. The management very much depends on the clinical situation of the individual patient.

Failing Grafts:

All patients with failing grafts should be assessed to determine their eligibility for a repeat transplant. (See section on eligibility for transplant). All patients who are felt to be eligible should be identified to the transplant centre and referred in a timely fashion to expedite an early review. Ideally eligible patients would receive a pre-emptive living donor transplant.

Patients who are Retransplant Candidates:

These patients should be referred back to their transplant center. At the time of referral a check of the level of PRA should be performed. The immunology lab should be notified of the incoming specimen. These results will guide the plan for immunosuppression in patients with failed grafts. Remaining on immunosuppression may prevent the formation of more anti HLA antibodies. This will improve their chances of retransplantation. It is especially critical in patients who have a compatible living donor. At the retransplant assessment patients will be given a plan for their ongoing immunosuppression which will be communicated to their attending nephrologist and documented in PROMIS. Ongoing orders or prescriptions can be provided by their dialysis physicians. Patients who are already highly sensitized will be given an immunosuppressive withdrawal plan. If symptoms develop they will require a transplant nephrectomy.

Patients who are not highly sensitized will hopefully receive an early transplant. If there is no potential for a living donor transplant after a year, and there is a prolonged projected wait time on the deceased donor list (blood group O or B), then consideration should be given to taper their immunosuppression slightly because of the significant long term risk without the corresponding benefits. This should be done in conjunction with their transplant center.

Patients who are not Retransplant Candidates:

Immunosuppression should be weaned in these patients. This is usually well tolerated but some patients may develop symptoms and will require a transplant nephrectomy.

Indications for Nephrectomy

- Acute rejection, unresponsive to therapy
- Life-threatening systemic disease caused by the transplant kidney (e.g. thrombocytopenia associated with rejection)
- Requirement to abruptly discontinue immunosuppression because of life-threatening illness (e.g. infection, malignancy)
- Symptoms related to the transplant kidney such as pain fever or hematuria.

Suggested Immunosuppressive Withdrawal Schedule

Day 0: Prednisone and antimetabolite (i.e. mycophenolate, mycophenolic acid or azathioprine) taper concurrently. If patient is on prednisone 5mg, continue current dose. If patient is on a prednisone dose higher than 5mg, decrease dose by 2.5mg every 2 weeks until 5mg is reached. Decrease antimetabolite (i.e. mycophenolate, azathioprine) dose by 50%.

Day 14 (end of week 2): Discontinue antimetabolite (i.e. mycophenolate, azathioprine).

Day 28 (end of week 4): Decrease calcineurin inhibitor/mTOR by 50% for 2 weeks. Patients may benefit by remaining on a small dose of prednisone, e.g. 5 mg daily or alternate days, for as long as their graft remains in situ.

Day 42 (end of week 6): Discontinue calcineurin inhibitor/mTOR. Patients may benefit by remaining on a small dose of prednisone, e.g. 5 mg daily or alternate days, for as long as their graft remains in situ

If a patient develops pain over their failed transplant and/or hematuria, they *may* respond to an increased dose of prednisone. Once the patient has responded to the steroids, the dialysis center should arrange for a transplant nephrectomy at the transplant centre.

3.14 Prophylactic Dental Coverage

Prophylactic Antibiotic Dental Coverage for Kidney Transplant Recipients

The American Heart Association Guidelines for the Prevention of Infective Endocarditis:

Recommend antibiotic prophylaxis before dental procedures ONLY for patients who have a history of previous infective endocarditis, or who have had cardiac valve replacement, or surgically constructed pulmonary shunts, or conduits. ([Journal of the American Heart Association, Circulation 2007; 116:1736-1754](#))

Prophylactic antibiotic coverage for dental procedures is recommended ONLY for the following transplant recipients:

- Prosthetic cardiac valve
- Previous infective endocarditis
- Congenital heart disease (CHD)
 - Unrepaired cyanotic CHD
 - 6 months following repair of CHD with any prosthetic material or device
 - Repaired CHD with residual defects
- Cardiac transplant recipients who develop cardiac valvulopathy

Recommended Antibiotic Regimens for a Dental Procedure

Situation	Antibiotic	Regimen: Single dose 30 to 60 min prior procedure	
		Adults	Children
Oral	Amoxicillin	2 grams	50 mg/kg
Unable to Take Oral Medication	Ampicillin	2 grams IV or IM	50 mg/kg IV or IM
	OR Cefazolin or Ceftriaxone	1 gram IV or IM	50 mg/kg IV or IM
True Allergy to Penicillin Allergic to Penicillin or Ampicillin – Oral	Cephalexin*#	2 grams	50 mg/kg
	OR Clindamycin	600 mg	20 mg/kg
	OR Azithromycin or Clarithromycin	500 mg	15 mg/kg
Allergic to Penicillin or Ampicillin and Unable to Take Oral Medication	Cefazolin or Ceftriaxone#	1 gm IV or IM	50 mg/kg IM or IV
	OR Clindamycin	600 mg IV or IM	20 mg/kg IV or IM

* Or other first or second generation oral cephalosporin in equivalent adult or pediatric dosage

Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema or urticaria with penicillin or ampicillin

3.15 SURGICAL PROPHYLAXIS

Transplant patients require prophylaxis for surgical procedures. The following are guidelines only. Prophylactic therapy must be tailored to the specific surgical procedure.

For clean operative procedures where prophylaxis is required primarily for skin organisms and the patient is **not** penicillin-allergic, use cefazolin (Ancef®), 1 gm IV on call to OR and then 1 gm IV q 12 h for 3 doses post-operatively.

If patients **are** penicillin-allergic, use clindamycin, 600 mg IV on call to OR and then 600 mg IV q 8h for 3 doses post-operatively.

For operative procedures with better gram negative coverage and where the patient is **not** penicillin-allergic, use of a third generation cephalosporin is recommended. Dosing is standard. Give one dose pre-operatively and 24 hours post-operative antibiotic coverage (exact dosing regimen depends on the cephalosporin selected).

3.16 DYSLIPIDEMIAS

Dyslipidemias are abnormalities in blood lipoproteins that are associated with an increased risk of cardiovascular diseases. Elevations of LDL-C are most closely associated with cardiovascular disease. The incidences and prevalence of dyslipidemia is high in kidney transplant recipients. As the overall prevalence of dyslipidemia during the first year post transplantation is greater than 50% all patients should be screened and monitored.

Statins are the proffered treatment for elevated LDL-C. There are interactions between CNI's and some statins so that drug dosage modifications may be required. There is a risk of rhabdomyolysis so that CPK should be monitored in all patients receiving statins.

Factors in kidney transplant recipients which may contribute to or cause dyslipidemias are immunosuppressive drugs (cyclosporine, sirolimus, prednisone), proteinuria, acute rejection and graft dysfunction.

(Refer to [Kidney Disease Improving Global Outcomes \(KDIGO\)](#), *Amer.J. Transpl. Vol 9, 2009, Pages S74-76*)

3.17 Phlebotomy

Phlebotomy is indicated for post-transplant polycythemia in male patients with refractory hemoglobin (Hgb) greater than 170 g/L and female patients with refractory Hgb greater than 165 g/L. Patients requiring frequent phlebotomy may benefit from treatment with an angiotensin converting enzyme inhibitor.

3.18 Immunization

Refer to most current BCCDC recommended Immunization of Special Populations Program as per [BCCDC Communicable Disease Control, Immunization Program, Section III - Immunization of Special Populations](#)

General Principles for Immunization of the Immunocompromised Patients

Maximize benefit while minimizing harm.

- There is potential for serious illness and death in the under-immunization of immunocompromised people and every effort should be made to ensure adequate protection through immunization.

Make no assumptions about susceptibility or protection.

- A history of childhood infection or previous vaccination may be irrelevant.

Vaccinate at the time when maximum immune response can be anticipated.

- Vaccines may be less effective when administered during the period of altered immunocompetence. Individuals who are fully immunized may remain at risk for vaccine-preventable diseases.
- Vaccinate early when immunologic decline is predictable.
- Delay vaccination if the immunodeficiency is transient (if this can be done safely).
- Primary health care provider may decide to stop or reduce immunosuppressive therapy to permit better vaccine response (if this is appropriate).

Consider the vaccination environment broadly.

- Vaccinate family and care givers when individuals need protection (i.e., against influenza).

Avoid live vaccines unless:

- Data are available to support their use and
- The risk of natural infection is greater than the risk of vaccination.

Administer routine boosters as indicated.

- The degree and duration of vaccine-induced immunity are often reduced in immune compromised individuals.

Consider the use of passive immunizing agents.

These include:

- Immune globulin (Ig)
- Intravenous immune globulin (IVIg)
- The several "pathogen-specific" Ig preparation that are available (i.e., varicella zoster Ig, tetanus Ig).

Ideally a solid organ transplant recipient should receive all vaccines before transplantation occurs. However some patients may not have been fully vaccinated prior to transplantation.

There is a potential for serious illness and death in both the under immunization and over immunization of solid organ transplant recipients. Immunization of those with significant immunodeficiency should be performed only in consultation with experts. Following transplantation

previous immunizations should be assessed and vaccinations offered to complete the schedule. Immunization should begin or resume at least six to twelve months after transplantation. If not vaccinated prior to kidney transplant patients should be immunized for:

- Td or Tdap
- IPV
- Hepatitis B
- Meningococcal (conjugate)
- Pneumococcal (conjugate and/or polysaccharide)
- Hib
- Influenza

Booster doses:

- Td every 10 years for life
- Influenza every year for life
- Pneumococcal once only revaccination after five years
- Meningococcal Polysaccharide every three years for life

All live vaccines (such as MMR and Varicella) are contraindicated following transplantation except in certain circumstances.

3.19 Contraception

Fertility greatly increases following a successful kidney transplant. Woman of child bearing potential should assume that they are fertile after transplant. Women are advised to avoid pregnancy in the first year after transplant. Barrier contraception is the method of choice (e.g., condom, spermicides and/or diaphragm). Oral contraceptives are generally not recommended, but may be used if the alternatives are not acceptable. IUD's are generally contraindicated in female transplant recipients.

3.20 PREGNANT TRANSPLANT RECIPIENTS

Plans for pregnancy should be discussed with the transplant team on an ongoing basis and the risks carefully explained. Factors associated with good outcomes for both mother and baby include, time post-transplant, good kidney function, absence of proteinuria and well controlled blood pressure.

Mycophenolate has been associated with a higher risk of birth defects. Women who wish to become pregnant should be switched from Mycophenolate to azathioprine three months before attempting pregnancy.

Pregnant transplant patients require close monitoring. All transplant pregnancies should be viewed as high risk, so the pregnant transplant recipient should be referred to an obstetrician who specializes in high-risk pregnancies. A working relationship between the transplant team and the obstetrician should be established. Transplant patients should be seen at frequent intervals during the third trimester, i.e., once per week.

Blood pressure should be well-controlled and women should be off drugs such as ACE inhibitors, which can cause fetal abnormalities. The safest antihypertensive drugs are methyldopa and beta blockers and calcium channel blockers.

The following are potential risks for the pregnant renal transplant recipient. Data is from the National Transplantation Pregnancy Registry (see reference below).

- Hypertension: Rates of hypertension for kidney recipients range between 50 to 70%. A fall in blood pressure during pregnancy may be seen as well
- Spontaneous abortions: Rates of spontaneous abortion range between 12% to 22% depending on immunosuppressive regimens
- Higher incidence of a pre-eclamptic-like syndrome characterized by hypertension, edema and proteinuria developing in the third trimester. Pre-eclampsia should be aggressively treated with hospitalization and urgent delivery if patients do not respond to more conservative means. Pre-eclampsia rates are approximately 30%
- Increase in incidence of premature (52 to 55%) and low birth weight (46 to 53%) infants
- Acute rejection rates during pregnancy range from 2% to 5%
- Diabetes during pregnancy rates range from 3% to 12%

Following pregnancy women may wish to breast feed. Anti-rejection drugs including tacrolimus and cyclosporine are found in breast milk but it is not known if these small quantities are harmful.

(Refer to [Kidney Disease Improving Global Outcomes \(KDIGO\)](#), *American Journal of Transplantation*, Supplement 3, Vol. 9, 2009 Pages S106-9)

3.21 ERYTHROCYTE STIMULATING AGENTS

Patients with chronic kidney disease often have impaired erythropoiesis. Erythropoietin and darbepoetin (referred to as erythrocyte stimulating agents ESAs) stimulate erythropoiesis in anemic patients with chronic renal failure. The same is true for renal transplant recipients with impaired graft function. It is important to note that there are many causes of anemia in transplant recipients other than poor kidney function which should be excluded before considering treatment with an ESA. It is critical to replete iron stores before beginning an ESA. As there are significant risks associated with ESA use the risk benefit ratio should be carefully considered and target hemoglobin values with treatment should not generally be higher than 110. Regular administration of erythropoietin or darbepoetin results in an increase in the reticulocyte count within two weeks with erythropoietin and within four weeks with darbepoetin, followed by an increase in the red cell count, hemoglobin and hematocrit. BC Transplant fax form must be sent to BC Transplant for approval prior to beginning therapy. See Appendix VI: [BCT Fax Form: Application for Erythrocyte Stimulating Agents](#)

(Refer to Clinical Guidelines for [Transplant Medications](#) for more specific information)

Laboratory Monitoring Schedule

When erythropoietin or darbepoetin therapy is initiated or adjusted the hemoglobin should be followed weekly until stabilized. If there is insufficient response after eight weeks of therapy, increase the dosage every two weeks until a target range of 95 to 110g is achieved. After the initial stabilization period, monitor patients monthly.

<i>Laboratory Monitoring Schedule</i>		
<i>Time</i>	<i>Labwork</i>	<i>Other Findings</i>
Baseline (before ESA's)	Vitamin B12, RBC folate, iron, TIBC, % saturation, ferritin, reticulocyte count, CBC, differential, BUN, creatinine, electrolytes	Blood pressure
Every two weeks for eight weeks	CBC and reticulocyte count	Blood pressure, Possible adverse effects of ESA's,
Monthly (while on ESA's)	CBC, reticulocyte count, BUN, creatinine and electrolytes	Changes to antihypertensives Same as above
Every three months	Regular monthly bloodwork, iron, TIBC, % saturation, ferritin/transferrin	

APPENDICES

List of Appendices**	
Appendix I	PROMIS TB Screening Questionnaire
Appendix II	Deceased Donor Wait List for a Kidney Transplant
Appendix III	Kidney Transplant Clinic Deceased Donor Wait List Agreement
Appendix IV	Exceptional Distribution Form
Appendix V	Recommended Follow-up Testing for Recipients Transplanted under Risk for Viral Mediated Disease Transmission
Appendix VI	BCT Fax Form: Application for Erythrocyte Stimulating Agents
Appendix VII	Antibody Mediated Rejection Protocol

**Forms may be revised periodically. Ensure you are using the most current version available.

APPENDIX I

PROMIS TB Screening Questionnaire

PROMIS TB Screening Questionnaire

Patient
 PHN: Name: DOB: Age: Sex: Selection Mode: Single Pat.

TB Screening Questionnaire

Assessment Date: Last modified by: 5. COMMENTS:

1. GENERAL

1.1. Country of Birth: 1.8. Have you ever had active TB?

1.2. Year immigrated to Canada: 1.9. If you had TB, was it treated?

1.3. Ethnicity: 1.10. Have you lived with or been in close contact with someone who had active TB?

1.4. Other, Specify:

1.5. Year started dialysis:

1.6. Are you Diabetic?

1.7. Are you on insulin?

2. SYMPTOMS

Have you experienced any of the following symptoms within the past year?

2.1. Cough (with or without phlegm) for > 3 weeks

2.2. Coughing up blood

2.3. Chest pain

2.4. Shortness of breath

2.5. Unexplained fever

2.6. Unexplained excessive night sweats

2.7. Unexplained weight loss

2.8. Unexplained excessive fatigue

3. TB TESTING

3.1. Have you ever had a TB skin test?

3.2. What was the result?

3.3. Do you have a written proof of TB skin test?

3.4. Have you ever received BCG vaccination?

3.5. Have you ever had abnormal chest x-ray?

4. CONSIDERING THE LIST OF COUNTRIES/CONTINENTS BELOW:

a) Africa (any country)
 b) Asia (China, Mongolia, Vietnam, Korea, Indonesia, India, Pakistan, Bangladesh, India)
 c) Europe (any country of former Soviet Union)
 d) Latin America (any country)
 e) Caribbean Islands (Jamaica, Dominican Republic, Haiti, Cuba, Trinidad)
 f) Pacific Islands including the Philippines and excluding Hawaii

4.1. Were you born in any one of these countries?

4.2. Have you ever stayed/visited in one of these countries for more than 1 month?

4.3. Have you ever lived or been in close contact with someone who lived in any of these places for more than 1 month?

Save Exit



Deceased Donor Wait List for a Kidney Transplant

Why should I go on it?

The kidney transplant team believes that a kidney transplant is a good treatment option for you. A person can get a new kidney in one of two ways – from a living donor or from someone who has died.

We understand at this point in your care that getting a kidney from a living donor is not an option for you. We believe you should consider going on the Wait List for a kidney from someone who has died. We realize this option comes with some questions and concerns. We want to make sure you understand what it means to be on the Wait List for a kidney from someone who has died. (This person is called a 'deceased donor'.)

Deceased Donor

A deceased donor is someone who has died very recently in the hospital. The person has died from a severe injury to the brain. For example, the brain injury could be from a stroke or a car accident. The person's brain no longer works and is considered 'brain dead'. Or the person may have died because the heart has stopped beating. This is called a non-heart beating donor. Either way, organs such as kidneys can be safely transplanted.

This information is meant to help you decide whether or not you want to be on the Wait List for a kidney from deceased donor.

What are the risks to getting a kidney from a deceased donor?

Many people ask us about the donor – how do we know the kidney is a good one? While we cannot guarantee that a donor kidney is 100% free of disease, our goal is to make sure donated kidneys are of good quality and safe for those who receive them.

We do the following checks of the donor:

- We do a thorough check of the donor's medical and social history.
- We screen the donor's blood for infectious and other diseases that we know can be passed on through the donor's kidney.

Note: Even when tests do not show any disease, there is still a remote chance that an infectious disease (such as hepatitis and HIV) or cancer could be passed on to the person receiving the kidney.

Even though we always test the donor's blood before any transplant, there can be times when we do not have all the test results before the transplant surgery is done. We let you know if this is the case. There is one test - the test for syphilis (a sexually-transmitted disease) - that can only be done on week days. Should this happen, the laboratory sends the result as soon as it is available. Luckily, the chance of donors having this disease is very low. If the result is positive for syphilis, you need to know this disease is easily treated with antibiotics. We would start you on antibiotics right away.

Sometimes we have donors who are at risk for having an infectious disease based on their medical history or lifestyle, yet all tests come back negative. Depending on what kind of risk it is, we may offer you the kidney anyway. The risk of you getting the disease is still very low, but not as low as a donor kidney without this risk.

The time to think about the risks is now. It is much harder to think about this at the time of being offered the kidney. Think about whether you are okay with accepting a kidney where there is a small chance of getting a disease. Write down your questions. Talk to your kidney specialist or a nurse from the transplant team. Think about what you are willing to accept and what you are not so when the offer comes, you are sure about your choice to accept the kidney or not.

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Deceased Donor Wait List - *continued*

How does the Wait List work?

Where you are placed on the Wait List depends on a few factors.

1. You are placed on the list that matches your blood type.
2. You move up the list depending on how long you have been on dialysis. This is based on the date you started your dialysis. This means the longer you have been on dialysis, the higher up the list you can move.
3. Another factor is whether you and the donor kidney are a good match. To check this, we check both your blood and the donor's blood type to make sure they match. We also check your blood for antibodies. If your body has antibodies against the donor's blood, the transplanted kidney would not survive (it would be rejected).
4. Not only do we match blood types and screen for antibodies, we also match you based on your age and the age of the donor. In some cases, certain people are given priority.

Here is how it works:

- If the donor is less than 35 years old...
We look for a child who is a good match first. If we do not find one, we look for an adult who is less than 55 years old.
- If the donor is between 36 and 59 years old...
We look at anyone who is a good match. If more than one person matches, we give the kidney to the person who has been on dialysis longer.
- If the donor is over 60 years old...
We first look at those people on the list who are also over 60 years old. If we do not find a match with this group, we then look at all the adults to see if there is a match.

You may be wondering why we target people who are over 60 years old to receive the kidney from an over 60 year old donor. Kidneys from older donors are the best choice for older patients. There is a good chance that an older donor's kidney will work until the end of the patients' life. A younger person needs a kidney from a younger donor. It is more likely that the younger donor kidney will work for the rest of the younger person's life.

FP.480.D355.PHC (Nov-10)

It can take a long time for you to move up the Wait List. Also, it can take a long time to find a donor kidney that is a good match for you. The Wait List process is fair for everyone who needs a kidney transplant.

What do I need to do to be on the Wait List?

- Since we never know when a good match might come up, we ask you to give us a blood sample each month.

We use this blood sample to compare possible kidney donors with you. We will give you the names of the special laboratories where you would go to give the blood sample.

- Please let your transplant nurse know if you have had a blood transfusion in the past.
- Do your best to stay healthy.

If you become ill, please let us know. For your health and the success of the transplant, you cannot have a transplant unless you are well enough.

Should you become ill, you do not lose your place on the list. Just let us know when your health improves so we can go back to looking for matches for you.

It's good to ask

If you have any questions about this process, please call or email us.

Tel: 604-806-9078 or 1-877-955-1755

Fax: 604-806-9658

Email: recipientnurse@providencehealth.bc.ca

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**KIDNEY TRANSPLANT CLINIC
DECEASED DONOR WAIT LIST
AGREEMENT**

I have read the information provided to me about the Deceased Donor Wait List and I understand how the Wait List works and how people on the list get a kidney.

I have had a chance to ask questions of the transplant doctors and other staff. They have answered all my questions clearly, using words I understand.

I, (printed name) _____, want my name to be put on the Wait List for a kidney from someone who has died (the Deceased Donor Wait List).

I agree to give a blood sample every month.

I agree to let my transplant nurse know if:

- I have moved
- I have been hospitalized or my health has changed
- I have had a recent blood transfusion

I understand that thorough testing is done of the donor before I get the kidney. However, I understand there are still risks to receiving a kidney from someone who has died (such as getting an infectious disease or other illness not found through testing).

I understand the test results of the donor's blood specifically for syphilis may not have come in before my transplant is done. I am willing to accept this risk knowing this disease can be treated with medicines.

Signature of patient Date & time of signature

Signature of MD Printed Name
obtaining consent

Signature of witness Printed Name (if MD not present)

Appendix IV Exceptional Distribution Form

	BC Transplant Exceptional Distribution Form
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PART A

Source Establishment: ☐ BC Transplant ☐ Other (Source Code) _____

Donor ID No.: _____ Date of Distribution of Organ: _____

Receiving Program or Transplant Centre: ☐ VGH ☐ SPH ☐ BCCH ☐ Ike Barber Lab
☐ Other _____

Name of Organ:
☐ Heart ☐ Lung (Dbl) ☐ Lung (Rt) ☐ Lung (Lt) ☐ Liver ☐ Pancreas ☐ Pancreas for Islets
☐ Kidney (Rt) ☐ Kidney (Lt) ☐ Adjunct Vessels Other Describe (e.g. small bowel): _____

Reason for Exceptional Distribution (include all tests not completed or conditions not met and risk of disease transmission). Refer to back of form:
Completed by: _____ Date: _____

PART B

TRANSPLANTING PHYSICIAN / SURGEON

The justification for acceptance is for compassionate reasons related to the interests of the recipient, including medical emergency and an organ determined safe is not immediately available.

I (or my authorized designate) have had a conversation with the recipient and/or next of kin/substitute decision maker in which I explained the reason(s) for Exceptional Distribution as defined above, and the risks associated with this reason(s). I have obtained informed consent from the recipient and/or next of kin/substitute decision maker and I authorize the acceptance of the organ(s) described above for transplant.

Name	Signature	Date	Time

THIS MUST BE FULLY COMPLETED WITH DATE AND TIME

Return completed signed copy to BCT Quality Assurance. FAX 604-877-2111

Doc.: RQA.04.016	Rev: 04	Eff Date: 01-Mar-2018	Ref Doc: RQA.02.018	CO#: 2018-536	Page 1 of 1
Copy 1 (white) - BCT Donor Chart Copy 2 (yellow) - QA Copy 3 (pink) - Sign and Return with Cooler Copy 4 (goldenrod) - Recipient Chart					



Recommended Follow-up Testing for Recipients Transplanted under EXCEPTIONAL DISTRIBUTION

NOTICE TO TRANSPLANT RECIPIENT MEDICAL TEAM

For Recipient: _____

You are receiving this notice because the donor for this recipient has evidence of: (✓)

- ☐ High Risk Behavior for Increased Risk of HIV, Hep B, Hep C
- ☐ Positive Hepatitis C Antibody Test with Negative RNA (NAT)
- ☐ Unknown Medical-Social History
- ☐ Other _____

IT IS RECOMMENDED THAT RECIPIENTS ARE TESTED FOR HIV, HEPATITIS B and HEPATITIS C AT:

4 weeks
3 months
1 year

Recommended Test Methods:

HIV serology (fourth generation Ag/Ab test)¹

HBV – HBV DNA (NAT), HBs Ag and anti-HBV core total antibody²

HCV – HCV Quantitative RNA (NAT)^{2**}

NOTES:

1. *If there is still concern for HIV despite a negative test, please consult medical microbiology about ordering an HIV NAT test.*
2. *Antibody testing is unreliable early post-transplant. It may be positive in the recipient for three to twelve months after transplant due to passive transfer of antibody with the transplanted organ. In addition, if the recipient has received cytomegalovirus immune globulin (CytoGam) or IVIG within the last 3 months, then PCR testing must be used over serology for HBV testing because of the risk of false positives.*
3. *Recipients with symptoms or laboratory evidence of reactivation (e.g. elevated liver enzymes) should be tested more frequently.*

For further information on these protocols, please contact Dr. Alissa Wright,
Transplant Infectious Diseases Specialist:

alissa.wright@ubc.ca / 604-875-4588



APPLICATION FOR ERYTHROPOIETIN/Eprex® or DARBEPOETIN/Aranesp®

Please fax form to BC Transplant at (604) 877-2111

Erythropoietin and darbepoetin are indicated for use in kidney/kidney pancreas transplant recipients who:

1. have a failing graft post transplant, or pre-transplant approved for transplant **and** are not on dialysis,
 2. **and** have one symptom of anemia (fatigue, exercise intolerance, angina, impaired cognition).
 3. **and** they must meet **ALL** the following lab criteria
 - i) glomerular filtration rate less than 50 mL/min by eGFR (based on MDRD equation)
 - ii) hemoglobin less than 95 g/L
 - iii) transferrin saturation (TSAT) 22% or greater
- All the lab criteria **MUST** be met before patient is initiated on Erythropoietin or Darbepoetin.
 - For more information on the BC Transplant guidelines for ESAs: click [here](#)

BCT ID #: _____	
Name: Last: _____	First: _____
Date of Birth: mo ____ day ____ year ____	Sex: male ____ female ____
Hospital: _____	Nephrologist: _____
Patient is: <input type="checkbox"/> on transplant wait list <input type="checkbox"/> post transplant has a failing graft	
Request for: <input type="checkbox"/> Erythropoietin (Eprex®) <input type="checkbox"/> Darbepoetin (Aranesp®)	
Weight: _____ kg *Hemoglobin: _____ g/L Serum Creatinine: _____ micromol/L *Creatinine Clearance/eGFR: _____ mL/min/1.73 m ² *Transferrin Saturation (TSAT): _____ % Serum Ferritin: _____ micromol/L *required data	
Physician's Signature: _____ Date: _____	
Approval by BCT: _____ Date: _____	
April 2017	



Antibody Mediated Rejection Treatment Protocol (updated Sept 2019)

1. Baseline Testing

- Renal function, kidney biopsy
- Donor specific antibody (DSA) testing
- CD19 and C20 subsets

2. AMR Treatment Protocol (Day 1-15, Day 1 = treatment start date)

I. Steroids:

- Pulse methylprednisolone 500 mg IV daily x 3 on Day 1,2,3 then prednisone taper as per standard protocol
- Example: Prednisone 100 mg x1 → 75 mg x1 → 60mg x1 → 50 mg x1 → 40 mg x1 → 30 mg x1 → 20 mg OD for 4 weeks then slow taper to 5 mg OD

II. PLEX and IVIG¹⁻³:

- PLEX + IVIG daily x 3 on Day 1,2,3 then 3 treatments per week for a minimum of 8 sessions. Additional treatments may be indicated based on clinical indication
- PLEX: 1.5x volume exchange for 3 treatments, then 1x volume exchanges thereafter. When performing PLEX within 48 hours of kidney biopsy replace with FFP, otherwise replacement with 5% albumin
- IVIG infusion: dosed 100 mg/kg/dose IV given after each PLEX
- Pre-medicate IVIG infusion with diphenhydramine 25-50 mg IV and acetaminophen 650 mg PO prior to IVIG

III. Rituximab (1-2 doses)⁴:

- Rituximab 375 mg/m²/dose IV given on Day 4 (could be given after PLEX and IVIG if there is adequate time and space)
- Pre-mediate Rituximab infusion with:
 - i. Diphenhydramine 50 mg PO/IV prior to Rituximab and Q4hr thereafter
 - ii. Acetaminophen 650 mg PO 30 min prior to Rituximab and Q4hr thereafter
- Wait for a minimum of 24 hrs (ideally 48 hrs) before resuming PLEX after dosing Rituximab
- Repeat CD19 and CD20 counts after last plex – if CD19/20 ≥ 5 cells/mm², consider giving a second dose of Rituximab

IV. Optimization of maintenance immunosuppression:

- Increase MMF or Myfortic to full dose (MMF 1g BID and Myfortic 720 mg BID)
- Up-shift CNI target one level up

V. Follow-up and Surveillance:

- Consider repeat kidney biopsy before 1-month post treatment based on clinical indication (i.e. inadequate treatment response, worsening renal function, re-assess mixed TCR and AMR); if patient has good clinical response, consider biopsy at 1 month or later
- Repeat DSA testing at Day 15 (after finishing 8 PLEX sessions), Day 28

Supplement 1: Diagnosis of AMR

- Refer to Banff 2013 Criteria for AMR diagnosis⁵
- A simplified schematic is provided in Table 1

*Note: C4d positivity is no longer required for AMR diagnosis as long as a significant degree of microvascular injury is present ($g+ptc \geq 2$)

*AMR treatment may be initiated if clinical and histologic evidence for AMR is strong and DSA and/or non-HLA antibody testing result is pending

	Acute/Active AMR	Chronic/Active AMR
Histology:	1. Microvascular injury: (g or ptc) 2. Arteritis 3. Thrombotic microangiopathy 4. ATN-unknown cause	1. Transplant glomerulopathy (cg) 2. Peritubular basement membrane duplication 3. Arterial intimal fibrosis
Serology:	Donor-specific antibodies (HLA, AT1R-Ab, MICA)	
Interaction:	C4d Moderate microvascular inflammation ($g+ptc \geq 2$) Endothelial cell gene transcripts	

Table 1. Simplified criteria for diagnosis of AMR, based on Banff 2013 classification⁵.

References

1. Montgomery RA, Zachary AA, Racusen LC, et al. Plasmapheresis and intravenous immune globulin provides effective rescue therapy for refractory humoral rejection and allows kidneys to be successfully transplanted into cross-match-positive recipients. *Transplantation*. 2000;70(6): 887-895.
2. Lefaucheur C, Nochy D, Andrade J, et al. Comparison of combination Plasmapheresis/IVIg/anti-CD20 versus high-dose IVIg in the treatment of antibody-mediated rejection. *Am J Transplant*. 2009;9(5): 1099-1107.
3. Sautenet B, Blanche G, Büchler M, et al. One-year Results of the Effects of Rituximab on Acute Antibody-Mediated Rejection in Renal Transplantation: RITUX ERAH, a Multicenter Double-blind Randomized Placebo-controlled Trial. *Transplantation*. 2016;100(2): 391-399.
4. Puisset F, White-Koning M, Kamar N, et al. Population pharmacokinetics of rituximab with or without plasmapheresis in kidney patients with antibody-mediated disease. *Br J Clin Pharmacol*. 2013;76(5): 734-740.
5. Haas M, Sis B, Racusen LC, et al. Banff 2013 meeting report: inclusion of c4d-negative antibody-mediated rejection and antibody-associated arterial lesions. *Am J Transplant*. 2014;14(2): 272-283.