ESPNT PROTOCOLS IN PEDIATRIC KIDNEY TRANSPLANTATION

The Egyptian Society of
Pediatric Nephrology &
Transplantation

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ESPNT protocols

in pediatric kidney transplantation

EDITED AND SUPERVISED BY

Prof. Fatina Fadel

Prof. Hafez Bazaraa

CONTRIBUTORS

Dr. Doaa Salah
Dr. Amr Salem
Dr. Eman Abou Bakr
Dr. Rasha Helmi
Dr. Mohamed AbdEl Mawla
Dr. Yasmin Ramadan
Dr. Yosra AbouEl Naga
Dr. Shimaa Sayed
Dr. Eman Fathy
Dr. Fatma Ateya
Dr. Shorouk AbdEl Rahman
Dr. Eman El Shenoufi

SURGICAL GUIDELINES

Supervised by
Prof. Hany Abd El Raouf

Prepared by
Dr. Mohamed Salah

PREFACE

To practice as a quality physician, you have to approach any problem you face in a scientific way. In this respect, working through protocols and guidelines is the ideal methodology to achieve this target, since they provide a framework that simplifies the approach for the vast majority of patients, that enables junior practitioners to benefit from previously established practice recommendations and that improves the standardization and harmonization of practice.

Transplantation is an integral aspect of pediatric nephrology that still has a significant demand and potential for expansion in Egypt and is one of the major goals of our society. In this regard, we wish that these transplantation guidelines would be helpful for our pediatric nephrology centers, pediatric nephrologists and patients.

Hoping to cover more and more of the field of pediatric nephrology in our protocols and guidelines.

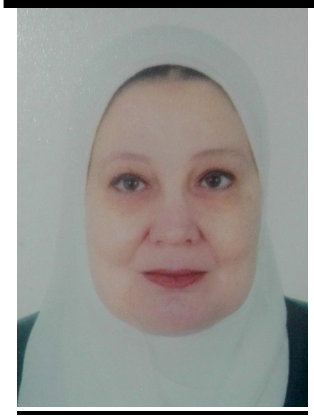
Best regards

Prof. Ramzi El Baroudi

Professor of Pediatric Nephrology, Cairo University

ESPNT President

PREFACE



The Egyptian Society of Pediatric Nephrology and Transplantation has took up the hard but essential task of producing protocols and guidelines that could facilitate and improve pediatric nephrology practice. In this regard, we attempted to present concise yet informative guidelines that cover the main aspects of transplantation. These reflect the current evidence-based recommendations as well as the necessary adaptations pertinent to the Egyptian pediatric nephrology community.

This is the product of a collaborative teamwork that includes members of our transplantation team, each of whom had a remarkable contribution. Transplantation is an interdisciplinary process and we felt it necessary to include a section on surgical guidelines by the pediatric urology team. We also wish to thank our professors, colleagues, institutions and everyone who has contributed to the success of the pediatric transplantation program.

Editors

Prof. Fatina Fadel

Professor of Pediatric Nephrology,

Head of Pediatric Nephrology Unit,

Pediatric Kidney Transplantation program director,

Cairo University

Prof. Hafez Bazaraa

Professor of Pediatric Nephrology,

Pediatric Kidney Transplantation program coordinator,

Cairo University

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MAIN SOURCE DOCUMENTS CONSULTED

KDIGO transplantation guidelines

Canadian guidelines: clinical guidelines for kidney transplantation (Vancouver coastal health, Providence heath care, BC transplantation)

British transplantation society and The renal association, UK guidelines

ERA-EDTA guidelines

Cochrane database of systematic reviews (Steroid withdrawal and CMV infection)

UpToDate (general principles of kidney transplantation in children, evaluation of recipient, evaluation of living donor, HLA matching, differential diagnosis of graft dysfunction, infections)

Nottingham children's hospital protocol

Lau K et al. Management of children after renal transplantation: highlights for general pediatricians (Review article). Transl Pediatr. 2012;1:35-

ABBREVIATIONS

ABMR: antibody-mediated rejection
AR: acute rejection
AZA: azathioprine
CAI: chronic allograft injury
CNIs: calcineurin inhibitors
CsA: cyclosporine A
DGF: delayed graft function
IVIG: intravenous immunoglobulin
KTRs: Kidney transplant recipients
MMF: mycophenolate mofetil
MPA/ MPS: mycophenolic acid/ sodium
mTORi: mammalian target of rapamycin inhibitors
NAT: nucleic acid testing
NCA: nurse-controlled analgesia
PCA: patient -controlled analgesia
PE: plasma exchange
PTLD: post-transplant lynphoproliferative disease
SCC: squamous cell carcinoma
SMX-TMP: sulphamethoxazole-trimethoprim
TAC: tacrolimus

A RECOMMENDATION:
shall be used to refer to a higher level of evidence where it should apply to most patients in the situation

A SUGGESTION:
shall be used to refer to a lower level of evidence where there may be more than occasional exceptions and the issue may still be the subject of considerable variation and/ or requirement for the establishment of higher/ more specific research evidence

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1. INDICATIONS OF RENAL TRANSPLANTATION

We recommend that kidney transplantation should be the renal replacement therapy of choice for the patient with chronic kidney disease stage 5 (ESRD) who is considered fit for major surgery and for chronic immunosuppression

General criteria

1. No active malignancy or infection
2. Absence of systemic disease which would severely limit rehabilitation
3. Life expectancy greater than 5 years with a successful transplant
4. Reasonable risk of graft loss or recurrence
5. Effective family or social support systems
6. Willingness to comply with treatment and follow-up requirements

Contraindications of renal transplantation

1. Active malignancy
2. Active infection
3. Severe respiratory, cardiac, vascular, hepatic or neurological conditions
4. Absolute risk of recurrence
5. Active drug or alcohol addiction
6. Patient non-adherence to therapy

Timing of renal transplantation:

We recommend that transplantation be targeted just before, at, or shortly (<6Mo) after the time when initiation of maintenance dialysis is required

However, transplantation can still be performed in those on longer-term dialysis

Patient size:

We suggest that recipients weigh at least 10 Kg at the time of transplantation

Etiology of ESRD:

We recommend that the etiology of ESRD be identified whenever possible.

This is particularly relevant to conditions associated with increased risk of recurrence or graft loss, such as primary hyperoxaluria, sporadic FSGS, MPGN, aHUS, Alport syndrome and lower urinary tract abnormalities

Transplantation team:

Transplantation is a multidisciplinary therapy that involves multiple specialties

2. PREPARATION FOR TRANSPLANTATION GUIDELINES

Recipient:

Patient education

We recommend that patients/ parents be educated regarding:

1. Transplant process
2. Risks and benefits
3. Medication regimen
4. Lifestyle adjustments
5. Effect of transplantation on existing medical conditions
6. Short and long term outcomes

Patient Investigations

The following routine investigations are recommended:

Laboratory

• ABO , Rh blood group, A subgroup
• HLA Typing Class I and II (A, B, DR)
• Panel-reactive antibodies

• Complete Blood Count
• Fasting blood Glucose, Lipid studies (total cholesterol, triglyceride, LDL, HDL)
• Sodium, Potassium, Calcium, phosphorous, alkaline phosphatase, ALT, urea, creatinine, uric acid,
• Total bilirubin, direct bilirubin, albumin and total proteins

• Urine analysis, culture and sensitivity and acid fast bacilli in urine
• Quantitative assay of proteinuria

• HBsAg &HBsAb, hepatitis C PCR, CMV IgG, EBV IgG, HIV I ,II

Radiology Studies

• Chest X-ray
• 12 lead Electrocardiogram
• Echocardiography
• Ultrasound of the native kidneys
• Aorto-iliac and IVC Doppler
• Voiding cystourethrogram (to evaluate for urethral patency, vesicoureteral reflux, bladder and residual urine volume). Urodynamic studies may be needed

Patients who are HBsAg negative and HBsAB negative should be vaccinated against hepatitis B. 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.

All patients will be screened for evidence of hepatitis C infection. HCV PCR is suggested. Positive patients will be referred to a hepatologist for further evaluation and consideration of therapy.

HIV positivity is a relative contraindication for kidney transplantation. Some HIV positive patients may be eligible with certain conditions.

Pre-transplant immunization

We recommend that all potential transplant recipients should have been immunized before transplantation.
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.

Patients should receive/ have completed the following vaccinations prior to transplant:
- Td or Tdap
- Hepatitis B
- Meningococcal (conjugate)
- Pneumococcal (conjugate and/or polysaccharide)
- Hib
- Poliomyelitis
- Influenza
- MMR
- Varicella

Live vaccines (OPV, 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 and can be given starting one month after transplantation

Other indicated non-live vaccines may be given starting six months after transplantation

Condition Update Report

We recommend that, if transplant was delayed, condition must be updated including:
- 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

Donor:

Only living donation is currently implemented in Egypt

We recommend that living-related donors are preferable, with appropriate consideration in case of inherited diseases

We recommend that, 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

The following donor work-up is recommended

Laboratory

• Blood group, Rh type and A subgroup (if recipient is A2 or A2B)
• HLA Typing Class I and II (A,B,DR)
• Cross-match with recipient by lymphocytoxicity assay or flow cytometry/ luminex
• Complete Blood Count
• Fasting blood Glucose, Lipid studies (total cholesterol, triglyceride, LDL, HDL)
• Sodium, Potassium, Calcium, phosphorous, alkaline phosphatase, ALT, urea, creatinine, uric acid
• Total bilirubin, direct bilirubin, albumin and total protein
• Urine analysis, microalbumin, culture and acid-fast bacilli
• 24 hour urine for creatinine clearance
• HBsAg, HCV-AB, CMV IgG, EBV IgG, HIV I ,II

Radiology Studies

• Chest X-ray
• 12 lead Electrocardiogram
• Echocardiography
• Pelviabdominal Ultrasound
• Renal isotopic scan
• CT angiography with excretory IVP

3. PERIOPERATIVE MANAGEMENT GUIDELINES

PRIOR TO HOSPITAL ADMISSION:

The following is recommended starting prior to hospital admission for transplantation:

- Cross-match must be negative within 7 days of surgery

- Cultures should be obtained when needed

- Immunosuppression may be started

- All consents and approvals must be obtained

- 3-4 units of blood/ packed PBCs should be typed and matched for each of the donor and recipient. *All blood should be leuko-depleted (washed and filtered, or irradiated and given by leukocyte filter)*

- Pretransplant dialysis:

Patients not on dialysis:
Dialysis may be indicated in some transplant candidates to correct metabolic abnormalities that cannot be treated conservatively or pose unacceptable anesthesia risk. Hyperkalemia is the most common reason for dialysis in the pretransplant period.

Patients on HD:
Hemodialysis on the day preceding transplantation is recommended.
Immediate pre-operative hemodialysis may initiate a pro-inflammatory state, delay surgery, increase the risk of DGF and excessively reduce serum potassium .

Patients on PD:
After admission, drain off PD fluid (only send for culture if cloudy) and remove PD catheter exit site dressing.
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.

- Vascular access:

A preoperatively inserted central line, usually a percutaneous dual/triple lumen catheter, is recommended for all children.

A central venous catheter in place for HD may be used provided it is not potentially infected. Temporary catheters may be exchanged if they have been indwelling for a significant period to make colonization likely (2 weeks).
If the patient is undergoing **pre-emptive transplantation** with no peritoneal or vascular access, then a jugular venous catheter suitable for haemodialysis should be considered

An arterial line is suggested to be inserted in the operating theatre.

HOSPITAL ADMISSION:

We recommend admission on the day prior to transplantation. Upon admission, a full medical assessment, including review of preoperative investigations, is recommended

1. We recommend the following to be checked and recorded on admission:

-Established time of surgery

-Physical state in general and fluid balance in particular to ensure adequate fluid repletion and absence of infection. Record approximate 24 hour urine output.

-Patients may be hypovolaemic if recently dialysed or hypervolaemic if in need of dialysis.

-Patients should NOT be dry and it is suggested to keep patients at or slightly above the dry weight.

-Maintenance fluids may be suggested in case of prolonged fasting when patients are passing significant urine.

-Blood pressure and 95th centile; based on the child's height and sex.

-Height and weight and calculate body surface area.

-Record the Donor and Recipient CMV and EBV status clearly in the case notes.

-Mark the NON-dominant wrist / forearm - "Do not use for arterial line"

-Fluid, medication and NPO orders. Clear non fizzy oral fluids may be allowed until 2 hours pre-operative

2. The following pre-operative investigations are recommended:

- CBC, PT and PTT
- Electrolytes, acid-base status
- Serum creatinine, albumin and ALT
- Chest X-ray
- 12-lead electrocardiogram

When done shortly before admission, only electrolytes and acid-base are recommended to be rechecked, as well as a chest X-ray if a new central line has been inserted/ attempted

3. We recommend that if a severe medical problem is identified at this time, the transplant will need to be postponed

4. Prophylactic antibiotics are recommended. Choices include Co-Amoxiclav, 3rd generation cephalosporins and Piperacillin/Tazobactam

If patient is known to be colonised with bacteria, then alternative antibiotics may be chosen based on sensitivity.

It is suggested to limit the duration of prophylactic antibiotics to the minimum time possible

5. We recommend the application of a pre-operative checklist that includes confirmation of:

- Explanation of the procedure and appropriate consents and approvals
- Completion of clinical assessment, investigations & blood booking
- A negative cross-match
- Vascular access and dialysis requirements
- Surgical preparation
- Last meal time/ NPO orders
- Medications, especially immunosuppressives and antibiotics

POST-OPERATIVE CARE:

We recommend that post-operative care be initially provided in a high-dependency unit, unless intensive care is required. A single patient room or cubicle is always required

Monitoring and Recording

The following is recommended:

1. Vital signs; pulse, respiratory rate, oxygen saturation,,blood pressure, CVP, core - peripheral temperature gap and urine output hourly initially.
2. Intra-operative input and output is recorded and the urine/ drain bags emptied for initiating fluid balance.
3. During the first 24hrs, blood pressure is recommended to be maintained at or slightly above the upper limit of normal and CVP of 10-15 cmH2O to maintain adequate graft perfusion

Investigations

1. Initial blood gases, Na, K, glucose, creatinine, albumin, Ca, P, Mg, CBC, PT, PTT
- These must be repeated daily for the first days until stable
- Bicarbonate, Na, K, glucose and HB must be repeated initially at least every 4-6h
- Bedside blood glucose should be monitored initially hourly
- Spacing/ more frequent reassessment will be determined according to needs

2. Post-operative CXR for patients with new central venous catheter. X rays when indicated
3. Post-operative graft ultrasound with Doppler, repeated whenever graft dysfunction or collections are suspected and before discharge
3. Drain HB/ creatinine may be checked if bleeding or prolonged excessive drain output (? Urinary leak) respectively
4. Tacrolimus/ Cyclosporine trough levels pre-morning dose. Usually monitored 2-3 times a week. Samples must be sent on EDTA and kept refrigerated until sent. The prescribed dose should be given once the sample has been taken; there is no need to wait for the result.
5. Complete liver functions should be done once-twice weekly
6. Cultures should be obtained whenever infection is suspected (blood, urine, others as needed)

Post-operative Fluid Regimen:

We recommend that fluid management target the following:

- Adequate BP, CVP and hydration
- Replacement of insensible losses, 100% of urine volume and any other losses
- After the first 24-48h: replacement of 80% of losses may be appropriate if the patient is passing adequate urine, maintaining normal hydration and CVP, and not excessively accumulating an undesired negative balance (i.e. urine concentration & oral intake gradually match decreasing IV replacement)

We recommend the frequent (initially hourly) assessment of fluid needs and adjustment of fluid orders accordingly

In patients with adequate diuresis, we recommend replacement of insensible and urinary losses with:
- 1:1 glucose 5%: normal saline
- Half-normal saline, with or without a separate replacement of insensible losses with glucose 10%, if hyperglycemia is a concern
- Sodium content should be increased if needed guided by Na monitoring (eg 2:1 saline: glucose, or normal saline)

- Non-urinary (NG, drain & wound) losses should be replaced with normal saline

- Potassium should be added and adjusted according to serum K (starting with a concentration around 8 mmol/L in given fluids)

- Hemoglobin should be kept at least 7-8 g/dL

- Capillary leak, low CVP associated with oedema or +ve balance should be corrected by albumin administration

- Fluid boluses to correct hypotension or hypovolemia should consist of normal saline if albumin or blood are not needed

- Hyponatremia or hypokalemia must be corrected

- Bicarbonate, phosphorous, magnesium and calcium may need to be supplemented

- Low-dose furosemide may be used when there is unexplained reduction in urine output with adequate or high CVP

- In the immediate postoperative period, hyperglycemia should be controlled with an intravenous infusion of insulin.

- The use of dopamine or mannitol to promote diuresis or improve graft perfusion is not recommended

- Fluids when there is Delayed or No Graft Function:

- In absence of fluid overload, replacement of insensible losses and urine (if any) is recommended. Insensible losses are initially (first 24-48h) replaced with normal saline : 5-10% dextrose 1:1 at 40 ml/m2/h, then as usual (400 mL/m2/day glucose 10%)
- If there are signs of **fluid overload** with increasing respiratory rate and oxygen requirement then **fluid removal** may be required

Antihypertensives:

- Suggested agents for early postoperative acute hypertension are nifedipine and i.v. labetalol. Others may be used if necessary eg hydralazine, nitrates
- Suggested oral agents for control of post-operative hypertension include calcium channel blockers, beta blockers if good renal function and diuretics in volume dependent cases
- ACE inhibitors are contra-indicated in the immediate post-transplant period.

Thromboprophylaxis:

We recommend assessment of the risk for thrombosis in transplant recipients.

We suggest early ambulation in all cases, and consideration of additional mechanical and/ or pharmalogical measures based on relative risks of thrombosis and bleeding. Routine pharmacological prophylaxis is not recommended in low-risk living donor recipients.

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Mechanical therapy consists of early ambulation, graduated compression stockings (GCS) and intermittent pneumatic compression (IPC)

Pharmacological therapy includes low-dose unfractionated heparin (LDUH), adjusted-dose heparin, low molecular weight heparin (LMWH).

Peri-operative administration (in agreement with surgeon) until mobilizing well (for 5 days in most cases), ''to be replaced by antiplatelet agents if indicated'' reduces peri-operative risk of venous thrombosis (including in ileo-femoral and renal veins), however, there may be associated increased blood loss.

A careful examination of coagulopathies in patients at risk in order to prevent early post-transplant thrombotic events is recommended.

Dose adjustment and monitoring (PTT/ anti Xa) will be required for patients with delayed graft function.

Pain management:

Appropriate assessment and control of post-operative pain is recommended.

Options include:
- Epidural analgesia
- Systemic opioids (including NCA and PCA)
- Multimodal analgesia (eg paracetamol iv with opioid supplementation)

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.

Wound Care:

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

Removal of Catheters and Drains:

After consultation with the surgeon:

1. Drain usually removed 1 - 3 days unless there is persistent drainage
2. Urethral catheter 5 - 7 days
3. Ureteric stent removal is planned (3-4 weeks).
4. PD catheters and/or gastrostomies not usually removed until 4 – 8 weeks post transplant (long-term gastrostomies may be in situ until oral feeding well established)

DISCHARGE PLAN:

Individualised for each patient/family.

- All patients should have ultrasound of transplant prior to discharge.
- Education program completed, ie drugs, monitoring, rejection signs, etc.
- Monitoring sheets in a folder/book.
- Return visits to ward/clinic (twice weekly initially).
- Arrangements for any blood tests.
- Ongoing dietary advice continued.
- Referral to Clinical Psychology if problems perceived.
- Date for removal of ureteric stent, peritoneal dialysis catheter or haemodialysis line (if placed).

4. SURGICAL GUIDELINES

Approach for living-donor Nephrectomy:

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We suggest the laparoscopic approach for living-donor nephrectomy in established kidney transplant programs. Nevertheless, open surgery, preferably by a mini-incision approach, is also a valid option.

Laparoscopic living-donor nephrectomy is associated with similar rates of graft function and rejection, urological complications and patient and graft survival to open surgery. However, pain, analgesic requirements, hospital stay and time to return to work are significantly better for laparoscopic procedures.

Graft inspection, preparation and perfusion:

For living donors, in whom immediate kidney transplantation is planned, graft perfusion with crystalloid solution is sufficient.

Bench/back-table preparation is a crucial step in the transplantation process:
-The kidney must be inspected whilst on a sterile iced slush, removing peri-nephric fat when possible to permit inspection of the quality of the organ and to exclude exophytic renal tumors.
-Biopsy of the kidney on the back-table may be performed. Suspicious parenchymal lesions also require biopsy.
-The number, quality and integrity of renal vessels, arterial intima and ureter(s) should be established.
-Branches of the renal artery not going to the kidney or ureter(s) should be ligated. The length of the renal vein should be evaluated and renal vein branches should be secured/tied. The peri-pelvic and proximal peri-ureteral tissue in the 'golden triangle' should be preserved.
-Lymphatics at the renal hilum should be ligated.

Graft implantation and vascular anastomoses:

An extra-peritoneal approach to either iliac fossa is recommended for first or second transplants. There is no evidence to prefer placement of a left or right kidney into either iliac fossa.

Ligation of peri-iliac vessel lymphatics is recommended to minimize post-operative lymphocele.

End-to-side anastomosis of donor renal artery to recipient external and/or common iliac artery is recommended. The aorta may be used for small recipients.
The external or common iliac arteries are equally appropriate. The internal iliac artery is more frequently affected by atherosclerosis than the external or common iliac arteries. The site of the arterial anastomosis should avoid atheromatous plaques in the iliac artery and the condition of the arterial intima should be checked.

Pre-operative imaging is recommended, to establish patency of one iliac vein and the IVC, when there is a history suggesting previous iliac or femoral vein thrombosis.
An intra-operative unexpected finding of iliac vein and/or vena cava thrombosis may lead to abandonment of implantation. With pre-operative planning, native renal (orthotopic) or superior mesenteric vein or gonadal vein collaterals can be used.

A 5/0 and 6/0 non-absorbable mono-filament polypropylene suture(s) are used for the renal vein and renal artery anastomosis.
Despite this, there is no evidence to recommend one suturing technique over another.

Appropriate segments of iliac artery and vein should be mobilized to facilitate tension free vascular anastomoses and the final positioning of the graft.

Suggested techniques to manage a short renal vein include:
-Ligation of internal iliac vein(s) to elevate the iliac vein and avoid tension on the renal vein anastomosis.
-Transposition of the iliac artery and vein may enhance the position for the venous anastomosis.
-The right renal vein may be lengthened, using donor gonadal vein retrieved at donor nephrectomy or with recipient saphenous vein, although both require specific consent and the other options are preferred.

Suggested management when there are multiple renal arteries includes:
-A very small second artery (especially if supplying the upper pole) may be sacrificed.
-Two arteries can be implanted separately or, to achieve a single anastomosis, may be joined together (as a trouser graft, or with end-to-side anastomoses of a smaller to larger artery).
-A lower polar artery may be anastomosed to the inferior epigastric artery.
-In living donor grafts with three or more arteries, consideration should be given to alternate kidney donors. Alternatives include a combination of the above techniques or, after appropriate consent, use of recipient's explanted internal iliac artery graft or saphenous vein graft.

In third and subsequent transplants the surgical approach must be planned pre-operatively so that appropriate arterial inflow and venous outflow exists with adequate space to implant the new kidney.

Ureteric implantation recommendations:

The donor ureter should be kept as short as possible with peri-ureteric fat preserved to ensure adequate ureteric blood supply.

Mono-filament absorbable sutures should be used for the urinary anastomosis to prevent stone formation around the suture material.

A stent is recommended for the transplant ureteric anastomosis. The stent should be removed before 30 days posttransplant.
Although a second procedure is generally required for stent removal, stents reduce major urological complications, especially urinary leak. The optimal timing for stent removal has yet to be defined but if left over 30 days is associated with more UTIs.

Ureteric anastomotic techniques for recipients with no urological abnormality include extra (Lich-Gregoir) or intra (Ledbetter-Politano) vesical uretero-neo cystotomy and uretero-ureterostomy using native ureter.

An extra-vesical anastomosis is suggested to be on the posterior rather than anterior bladder. *Posterior bladder placement may be associated with less hydronephrosis post stent removal and facilitate future endoscopic manipulation if needed.*

Pyelo- or uretero-ureterostomy to the ipsilateral native ureter has been described as a primary technique in recipients with non-refluxing native ureters. In cases where

donor ureter has been damaged at retrieval then pyelonative- ureterostomy or pyelo-neo-cystotomy can be performed.

Duplex ureters can be anastomosed together and then joined to the bladder as one unit (double pant) or kept as two separate anastomoses. A single anastomosis with single cystostomy is suggested.

The following points should be considered when performing kidney transplantation in the abnormal urogenital tract:

- In patients with an ileal conduit, a kidney transplant may be placed upside down to align the ureter to the conduit and avoid a redundant ureter. Transplanted ureter is implantated into an ileal conduit similar to native ureter(s) (Bricker; Wallace).
- In bladder augmentation or continent pouches, ureters should be implanted with a tunnel technique or extra-vesically (Lich-Gregoir). The latter is favored in most patients.
- In patients with a Mitrofanoff catheterisable stoma or continent ileo-caecal pouch with catheterisable stoma, consideration should be given to the positioning of the catheterisable stoma so that the position of any future transplant kidney is not compromised.

Perioperative and surgical complications:

We recommend that the living donor be appropriately informed and managed to minimize, identify and deal with any complications.

Donor nephrectomy is generally a low-risk procedure. Donors are healthy individuals associated lower risks; however, the occurrence of any complications is less acceptable than in a patient.

Recipient complications

Hemorrhage

While most hematomas are small and asymptomatic; hence not requiring intervention, we recommend in the case of large hematomas, clinical signs and symptoms due to external pressure with graft dysfunction and/or thrombotic graft vessels complications:

-percutaneous drainage under computed tomography or ultrasound guidance

-surgical treatment if necessary,

Arterial thrombosis

Surgical exploration to evaluate the status of the graft is recommended. In the rare event the graft appears salvageable, a thrombectomy must be performed.

Alternatively, thrombolytic agent administration through a catheter directly into the transplant renal artery may be used after the first 10-14 post-transplantation days.

Venous thrombosis

Surgical exploration is usually recommended despite the fact that the majority of the cases will result in graft loss. When the graft is salvageable, surgical thrombectomy or explanation, bench reperfusion followed by re-implantation can be performed.

Thrombolytic agents can also be used; however, their results have not been satisfactory.

Transplant renal artery stenosis

We recommend that management be based on the hemodynamic significance of the stenosis:
-In cases of clinically significant stenosis (with symptoms or graft impairment) and/or > 50% stenosis on US-color-Doppler, a confirmatory angiogram should be performed.
-Interventional radiology with percutaneous transluminal angioplasty with or without stent placement is recommended for significant lesions.
-Patients considered unsuitable for radiological angioplasty due to recent transplant, multiple, long and narrow stenosis, or after failure of angioplasty may benefit from surgical treatment.

Arteriovenous fistulae and pseudo-aneurysms after renal biopsy

We recommend that persistent symptomatic AV fistulae (with hypertension, hematuria or graft dysfunction due to shunting) as well as enlarging pseudo-aneurysms (risk of rupture) be managed with angiographic selective or super selective embolization.
Partial or total allograft nephrectomy should be the last option.

Lymphocele

Suggested options for significant lymphoceles include:
- Placement of a percutaneous drain (i.e. Pig-Tail) under imaging guide
- Laparoscopic fenestration, associated with the lowest recurrence and complication rate compared to open surgery and aspiration therapy
Percutaneous aspiration can be performed although the recurrence and infection risks are high. Sclerosant agents such as ethanol, fibrin sealant, gentamicin, or octreotide reduce the recurrence rate compared to simple aspiration.

Urinary Leakage

Urinary leak can be suspected by the urine output and the creatinine level in the drain fluid.
In order to decrease the risk of ureteral necrosis, it is important to preserve vascularisation of the distal ureter. Furthermore, the routine use of JJ stent is recommended.

The management of urinary leak depends on the location (renal pelvis, proximal or distal ureter, and bladder), the time of appearance and the volume of the leak:
-For early and low volume urine leaks the treatment may be conservative.
-In case of failure of conservative management or massive leak, surgical repair is needed. Ureteral re-implantation directly to the bladder or to the native ureter provide similar results.

Ureteral Stenosis

Clinically significant ureteral stricture should be considered when persistent hydronephrosis on US occurs in association with impaired renal function.
Placement of a percutaneous nephrostomy and an antegrade pyelogram are initially recommended.

The subsequent treatment options depend on the timing, recoverable kidney function, length and anatomy of the stricture and recurrence; and generally include:
- endoscopic procedures (percutaneous balloon dilatation or endourological repair)
- surgery with direct re-implantation, pyelo-vesical re-implantation or uretero-ureterostomy.

Hematuria

Bladder irrigation is the first line of treatment. Some cases require cystoscopy with evacuation of clots and/or fulguration of bleeding sites.

Reflux and acute pyelonephritis

-Endoscopic injection of dextranomer/hyaluronic acid copolymer may be the first approach for treatment of vesicoureteral reflux associated with acute pyelonephritis.
-Ureteral re-implantation or pyelo-ureterostomy with the native ureter is a viable second treatment option.

Kidney stones

-In case of obstructive stones first-line treatment includes placement of a nephrostomy tube, or in some occasions a double J stent.

-Definitive treatment options include Extracorporeal shock wave lithotripsy (ESWL), ureteroscopy and percutaneous nephrolithotomy.
In cases of large impacted stones, uretero-ureteral anastomosis, pyelo-ureteral anastomosis or uretero-vesical re-implantation may provide excellent results for both stone and ureteral obstruction.

Wound infection

Subcutaneous sutures, pre-dialysis transplantation, sealing or ligation of lymphatic trunks, prophylactic fenestration, reducing corticosteroid load and avoiding sirolimus/everolimus therapy can decrease wound complication rates.

Incisional hernia

Open and laparoscopic repair approaches are safe and effective

5. IMMUNOSUPPRESSION GUIDELINES

The goal remains to maintain optimum level of immunosuppression
(i.e. minimize acute rejection (AR) and not to increase incidence of infection and malignancy)
with minimal toxicity.

We recommend that immunosuppressive therapy is based on the transplant immunological risk and concerns with individual agents.

Immunological risk stratification:

Immunological low risk:

- 1st time transplant recipients who have less than 20%* PRA and no DSA (by luminex).
- Repeat transplant recipients who have not aggressively rejected a previous transplant (i.e. not within the first year) & who have less than 20%* PRA and no DSA.

Immunological intermediate risk:

- Transplant recipients with PRA between 20%* & 80% and no DSA
- Rh incompatibility
- Repeated blood transfusions
- Previous (NOT current), not otherwise explained, +ve cross match (lymphocytotoxicity)/ DSA with the same donor

Immunological high risk:

- Transplant recipients who have rejected one or more transplants aggressively (within the 1st year posttransplantation)
- Any recipients with greater than 80% PRA.
- Transplant following any desensitization procedure

**** PRA >0% and <20% is sometimes considered intermediate risk***

We recommend that antibody induction therapy be used in all pediatric kidney transplant recipients. The first dose should be given intraoperatively prior to declamping

IL2 receptor antibody (Basiliximab) is suggested for patients with low or intermediate risk; in a dose of:

- 20 mg x 2 doses on day 0 and day 3-4 in recipients weighing > 35kg
- 20 mg in 1-2 divided doses in recipients weighing < 35kg

T cell depleting therapy *(ATG; 5-9mg/Kg or thymoglobulin; 1.5mg/Kg/d x 5d)* is recommended for induction in high immunological risk transplants and is not recommended in patients with increased risk of infection or malignancy

Maintenance immunosuppression with a calcineurin inhibitor (Tacrolimus or cyclosporine) and mycophenolate, with or without steroids, is recommended in most transplant recipients

In low risk transplants, steroid avoidance; with only perioperative steroids, tapered to elimination within the first week, may be used so long rejection has not occurred

Azathioprine is generally less immunosuppressive than mycophenolate and may be used in individual patients/ situations

We recommend NOT to use generic forms of immunosuppressive agents in KTRs

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Suggested use of steroids:

Methylprednisolone IV: 5-10 mg/Kg (150-250 mg/m2) up to 250 mg per dose

-The night before the operation -At the time of induction of anesthesia
-At the time of declampling -6 hours post-operative

- The same dose is given once on the day following operation and gradually tapered, converted to oral when tolerated and dose is 2-3 mg/Kg/day and reduced targeting 15-20 mg/m2 by day 14

- After the first month, dose is gradually tapered down to 2.5-7.5 mg/ day 6-12 months. Further management is individualized; however, late discontinuation always carries a risk of AR

Suggested use of Calcineurin inhibitors:

-May be started before up to the morning after Tx

-Be aware of food and drug interactions

-Tacrolimus is preferentially suggested in patients with dyslipidemia, significant hirsutism & in those who are considered immunological high risk

-Tacrolimus: is started in a dose of 0.15mg/kg/day in 2 divided doses

-Cyclosporine: is started in a dose of 8-10 mg/kg/day (250mg/m2/day) in 2-3 divided doses (3 in younger children)

-Both are adjusted to therapeutic ranges based on drug level monitoring:

-The suggested target trough level of Tacrolimus is 10-15 ng/mL in the first month and 5-10 ng/mL later (higher in the first 3-6 months)

-The suggested target trough level of Cyclosporine is 200-250 ng/mL in the first month, around 150 ng/mL up to 6 months and around 100 ng/mL therteafter

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Suggested use of Mycophenolate:

-Mycophenolate mofetil (MMF) or Mycophenolate sodium (MPS) may be used. Patients differ in tolerance

-Starting dose of MMF is 1200mg/m2 in 2 divided doses, starting 2 days preoperative
-Lower doses 900mg/m2 may be used with Tacrolimus
-Higher doses up to 1800mg/m2 may be used when needed (immunologically) & tolerated (hematologically & GIT)

The starting dose of MPS is 900mg/m2 in 2 divided doses

Mycophenolate should be separated from Tacrolimus or Cyclosporine by 2hrs

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Target of rapamycin inhibitors:

-mTORi (sirolimus or everolimus) based protocols may be used in low immunological risk patients.

-The loading dose of sirolimus is 3mg/m2 once followed by a maintenance of 1mg/m2 once daily in patients <40Kg. Adults/ larger patients receive 6mg loading and 2mg/day maintenance. Doses are adjusted to a target trough level of 5-15ng/mL

-The starting dose of everolimus is 0.6mg/m2/dose twice daily and target trough level is 3-8ng/mL

-They are not recommended in the first month

-They have advantages regarding lower risk with malignancy and certain infections as CMV

-They may cause/ increase proteinuria and dyslipidemia in a dose-dependent manner

-Everolimus allows reduction in CNI dose (60% with CsA and 40% with tacrolimus)

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6. ROUTINE FOLLOW UP SCHEDULE

	First month		First year			After first year
	First week	2nd- 4th week	2nd- 3rd month	4th-6th month	7th-12th month	
Clinical follow up[(a)]	Patient admitted	Twice per week	Every 1-2 weeks	Every 2-4 weeks	Monthly	Every 2–3 months
Serum creatinine	Daily	2 per week	Weekly	Every 2 weeks	Monthly	Every 2–3 months
CBC	Daily	2 per week	Weekly	Monthly		Annually
Fasting plasma glucose[(b)]	Weekly+ 2 hours pp at the end of 1st month		Every 3 months			Annually
HbA1c[(b)]			Once			Annually
Serum calcium & Phosphorus[(c)]	Daily until stable	Weekly until stable	Once	Once		Annually
ALP			Annually			
PTH[(d)]			Once	According to CKD-T stage		
ALT in HCV-infected patients[(e)]	Once		Once	Monthly		Every 3months
ALT in non-HCV-infected patients	Once		Every 3months		Annually	
Complete lipid profile			Once			Annually
CNI blood levels[(f)]	Every 3 days until target level reached		Once	Once		
Proteinuria in non-FSGS	Once		Every 3 months			Annually[(g)]
Proteinuria in FSGS	Daily	Weekly	Monthly	Every 3 months		Annually[(g)]
EBV PCR[(h)]		Once	Once	Once	Once	
BKV PCR				Once	Once	
Allograft ultrasound	Once	Weekly	Monthly			Annually
Allograft biopsy[(i)]		Once	3rd month		12th month	Annually?
Influenza vaccination			Annually			

CBC: complete blood picture, ALP: alkaline phosphatase, PTH: parathyroid hormone, CNI: calcineurin inhibitor, EBV: Epstein-Barr virus, PCR: polymerase chain reaction, BKV: BK polyoma virus, ALT: alanine aminotransferase, HCV: hepatitis C virus

(a) Clinical follow up after discharge every visit including measure of blood pressure, pulse, height, body weight, BMI, waist circumference when weight and physical appearance suggest obesity, but BMI is <35 kg/m^2 and head circumference every 3 months if child <3 years old
(b) Screening for new-onset diabetes in non-diabetic kidney transplantation recipients, known diabetics should be also, followed with HbA1c every 3 months
(c) CKD-T4: every 3–6 months, T5: every 1–3 months
(d) CKD T2-T3: once with subsequent intervals depending on baseline level and CKD progression, T4: every 6–12 months, T5: every 3–6 months
(e) Perform imaging annually to look for cirrhosis and hepatocellular carcinoma
(f) Whenever there is a change in medication or patient status that may affect blood levels; or whenever there is a decline in kidney function that may indicate nephrotoxicity or rejection
(g) Done every 3-6 months in HCV infected recipients
(h) EBV PCR for high-risk group with donor EBV seropositive/ recipient seronegative)
(i) when protocol biopsies are performed

CHEMOPROPHYLAXIS

	First year		
	First 3 months	4^{th}-6^{th} month	7^{th}-12^{th} month
CMV chemoprophylaxis*	Oral ganciclovir or valganciclovir		
CMV PCR**		Monthly	
Oral and esophageal Candida prophylaxis	Oral nystatin		
UTI / Pneumocystis Jirovecll pneumonia prophylaxis	Daily trimethoprim-sulfamethoxazole		

**All will receive CMV chemoprophylaxis except when donor and recipient both have negative CMV serologies with no any other risk*

*** When donor sero-positive and recipient sero-negative*

7. NUTRITION & GROWTH POST-TRANSPLANTATION

Nutritional risk factors

- *Preexisting malnutrition at the time of transplantation*
- *The need for catch-up growth*
- *Mineral and bone disease*
- *Effects of immunosuppressive medications (increased appetite with steroids, dyslipidemia, impaired glucose tolerance, etc)*
- *Risk of obesity and dyslipidemia*
- *The need to reduce cardiovasacular risk*

Nutritional recommendations

- **Generally a well-balanced healthy diet**
- **Caloric and protein intake depending on normal and catch-up growth needs and the need to prevent/ manage overweight**
- **All patients should be screened for dyslipidemia and impaired glucose tolerance**
- **Limitation of simple sugars, total fats, saturated fat, hydrogenated oils and fried foods**
- **Increase high-fiber foods as fiber improves GI function, helps keep cholesterol from being absorbed and avoid excessive weight gain in patients with increased appetite. Fresh fruits, vegetables, and whole-grain products are high-fiber foods**
- **Eating three meals a day with average helpings and avoid too much snacking. If necessary, use healthy low-fat snacks (eg raw vegetables, fruits, and unsalted, unbuttered popcorn).**
- **A healthy lifestyle with adequate physical activity (at least 30-60 min 6 days per week)**
- **Statins are the preferred 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 rhabdomyalysis so that CPK should be monitored in all patients receiving statins.**
- **Adequate vitamin D and calcium. Supplements (especially of vitamin D) may be needed**
- **Phosphorous restriction will generally be no longer necessary. Increasing phosphorous intake is commonly needed early after transplantation**
- **Normal potassium intake is generally required; however, calcineurin inhibitors and ACE inhibitors may increase potassium while steroids, loop diuretics and the presence of tubular dysfunction decrease potassium**
- **Modest sodium limitation, consistent with a generally healthy diet, is suggested**
- **A multivitamin/ mineral supplement with the RDA may be considered**
- **Patients with impaired graft function and anemia may benefit from treatment with erythropoiesis stimulating agents (erythropoietin or darbopoietin) when iron deficiency has been excluded/ corrected and other causes of anemia are addressed. When used, patients must be monitored weekly for hemoglobin response until stable then monthly.**

Practical points:

Heart-healthy food guidelines:
• Eating fruits and vegetables
• Choosing whole grains, lean meats and alternatives, low-fat dairy products, and unsaturated oils
• Avoid fat listed as animal or vegetable shortening, lard, palm, and coconut oil.
• Choose olive and canola oil, and non-hydrogenated margarines.
• Limiting foods high in salt, sugar, and saturated fat and low in nutrients.

Some good sources of calcium:
• Milk
• Cheese
• Yogurt
• Canned salmon or sardines with bones
• Calcium-fortified orange juice

The best sources of Phosphorous:
• Dairy products
• Nuts and nut butters
• Dried beans, lentils and peas
• Seeds

Some common foods that are HIGH in sodium are:
• Salt
• Cured meats (bacon, ham)
• Luncheon meats
• Canned or dried soups
• Ethnic foods: Chinese, Japanese, Mexican and Italian
• Sauces and condiments: Worcestershire, chili and soy
• Prepared casseroles, macaroni and cheese mixes

Growth after kidney transplantation

Children with chronic kidney disease commonly have growth failure. Growth may improve after successful transplantation; however, growth failure sometimes persists

All KTRs should be evaluated for anthropometric measurements and growth velocity

Before considering growth hormone therapy, patients should be assessed for adequate caloric and protein intake and for potential reduction of corticosteroid dose.

Growth hormone therapy may be considered for KTRs with growth failure *(height <3rd percentile or height target standard deviation score <−2 AND height velocity <25% for chronological age)* and growth potential.

Growth hormone is typically not started during the first 6 months post-transplantation. The following precautions should be considered:

- Patients with recent, difficult or repeated rejections should not receive GH
- Active malignancy is an absolute contraindication of rhGH therapy
- Bone deformity should be corrected before staring rhGH therapy, otherwise it could be exaggerated
- Any metabolic abnormality (as hypocalcemia, hypophosphatemia, hyperparathyroidism & metabolic acidosis) should be corrected before initiation of rhGH therapy
- Close monitoring of graft function is mandatory during rhGH therapy with discontinuation if rejection occurred

The recommended dose of GH is 28 IU/m2/week of rhGH (4 IU/m2/day; 0.05mg/Kg/day) by daily SC injection.

Baseline evaluation of graft function, MBD parameters, anthropometric assessment, target height, growth velocity, pubertal stage, bone age, hip X ray & fundus examination is needed prior to starting GH therapy. Anthropometry, growth velocity, Ca, P and PTH should be monitored q3Mo and bone age annually during therapy.

GH therapy should be discontinued when:

- Height end-point is achieved

- Epiphysis is closed

- Graft rejection occurs

- Slipped femoral epiphysis, severe hyper PTH, active malignancy, documented increased ICT, non-compliance.

8. RENAL ALLOGRAFT BIOPSY

Renal allograft biopsy is recommended in the following conditions:

1. There is a persistent (to avoid normal laboratory or physiological variability), unexplained {no dehydration, urinary obstruction or high blood levels of CNI}, increase in serum Creatinine (A 25–50% or 0.3 mg/dL increase over baseline).
2. Biopsy is preferably obtained before starting antirejection therapy provided it wouldn't delay therapy and when serum Creatinine has not returned to baseline after treatment of acute rejection with the first line to exclude a new pathological process, such as coexistent acute tubular necrosis, drug toxicity or BKV nephropathy.
3. Every 7–10 days while patients are receiving dialysis for delayed graft function as the incidence of acute rejection during DGF is higher than in patients without DGF and will not be recognized.
4. Expected kidney function is not achieved within the first 1–2 months after transplantation.
5. New onset or persistently unexplained Proteinuria more than 300mg/g.

Protocol biopsies:

Protocol biopsy is suggested to detect clinically inapparent (subclinical) acute rejection, chronic allograft injury and CNI nephrotoxicity. It can be done at 1, 3, and 12 months and then annually.

Treatment of subclinical rejection may improve outcomes.

NB: *Pretransplant kidney biopsy is used to judge the quality of a deceased donor organ at excision and, on occasion, to rule out the possibility of disease in live donors.*

Preparation of renal graft biopsy (as in native kidney biopsy):

Control of BP, CBC {platelet count >70-100,000/mm^3}, coagulation profile {INR<1.3} and bleeding time. Aspirin is withheld for 3 to 5 days prior to the biopsy and enoxaparin is withheld for 24 hours.

Technique of transplant renal biopsy:

Use of real-time ultrasound guidance in the performance of percutaneous renal allograft biopsy is universal.
All graft biopsies must be examined for C4d deposition by immunohistochemistry.

Complications of graft biopsy:

Hemorrhage is the predominant complication related to graft biopsy and may occur acutely as microscopic or gross hematuria or subcapsular hematoma, rarely cause graft loss. Arterial injury may also result in arteriovenous fistulae or a pseudoaneurysm.

9. ACUTE GRAFT DYSFUNCTION

***Definition**: Acute impairment of the graft functions usually manifesting as elevation of the serum creatinine by 25-50% or ≥0.3mg /dl of the baseline creatinine.*

'Acute graft failure' generally refers to more severe dysfunction

Causes :

***Pre renal :** dehydration ,volume depletion or sepsis.*

***Post renal :** Urinary tract obstruction*

***Renovascular** : as renal artery stenosis and renal vein thrombosis.*

***Renal intrinsic:** Acute rejection, Acute CNIs toxicity, Infection : as UTI, CMV or BK virus nephropathy, Others as recurrent and de novo renal disease presenting acutely*

We recommend that all transplant recipients be regularly monitored for graft function. Any unexplained rise in serum creatinine should be promptly evaluated and managed

We recommend that any patient presenting with acute graft dysfunction have the following factors assessed and corrected:

1. Volume and hydration status
2. Vascular lesion or urinary tract obstruction (graft ultrasound with Doppler)
3. Drug level (CNI): drug level must be checked and if necessary, adjusted. If CNI level has been too high, check creatinine response to reducing dose. A low CNI level may be associated with AR that may not be corrected simply by increasing the dose.
4. Systemic or UT infection
5. Other obvious causes

We recommend that graft biopsy be performed in any patient presenting with unexplained acute graft dysfunction.

We suggest that first-line antirejection therapy not be delayed awaiting extensive evaluation when AR is likely

10. ACUTE REJECTION

An acute rejection episode is an acute, potentially reversible, immune-mediated graft injury. It can be the consequence of a T cell &/or antibody-mediated immune response (it can be mixed)

Clinical AR generally presents as acute graft dysfunction (rising creatinine). Other manifestations include new-onset proteinuria or hypertension. Fever and graft tenderness are rare except in the context of low CNI.

Types of rejection according to timing:

- ***Hyperacute :*** *immediate*
- ***Accelerated AR :*** *first week*
- ***AR :*** *1 week to 3 months*
- ***Delayed AR :*** *3 months to years*

Treatment :

We recommend that all AR episodes be initially treated with pulse methylprednisolone (250 mg/m2 – 10 mg/Kg for three successive days).

We recommend that subclinical AR be treated

We suggest that first responsive AR episodes be followed by rapid tapering of oral steroids to or just above the maintenance dose, with optimizing trough CNI levels

We suggest that increased immunosuppression be considered for patients with rebound, recurrent, difficult or antibody-mediated ARs

AR is considered steroid resistant if there is no response 5-7 days after the first dose

We recommend T cell depleting therapy in all steroid-resistant acute T cell mediated rejections, and suggest its use in very early, severe (Banff IIb or above) or rebound cases

Options for ABMR include steroids, plasma exchange, Rituximab and IVIG:

-PE is suggested at 1.5 plasma volume daily x3, followed by 3 treatments per week at 1 plasma volume for a minimum total of 8 sessions. Additional treatments may be indicated based on condition. -Replacement is performed with 5% albumin unless plasma is otherwise indicated (coagulopathy and possibly within 48h of kidney biopsy)

-IVIG may be replaced at 100 mg/kg/dose given after each PE, 400 mg/Kg after the third session and/or be given in a total dose of 1-2g/Kg. The latter dose should be given after, not before, PE

-The recommended dose of Rituximab is 375 mg/m2/ dose for 2-4 doses at weekly- 2wk intervals. The first dose may be given after the third PE session; however, wait for a minimum of 24 hrs (ideally 48 hrs) before resuming PE after dosing Rituximab.

-We suggest intensifying baseline immunosuppression after treatment for ABMR

-We suggest premedication with steroids (100 mg/m2 methylprednisolone) 30 minutes before Rituximab or first (& possibly second) dose of T cell depleting antibodies
-We suggest premedicating Rituximab with (in addition to steroids) paracetamol and diphenhydramine (oral or IV) and continuing these medications for 24-48hrs
-We suggest premedicating T cell depleting antibodies (1st and 2nd doses) with (in addition to steroids) paracetamol and diphenhydramine (oral or IV)
-IVIG may be premedicated with diphenhydramine and acetaminophen

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11. CHRONIC GRAFT DYSFUNCTION

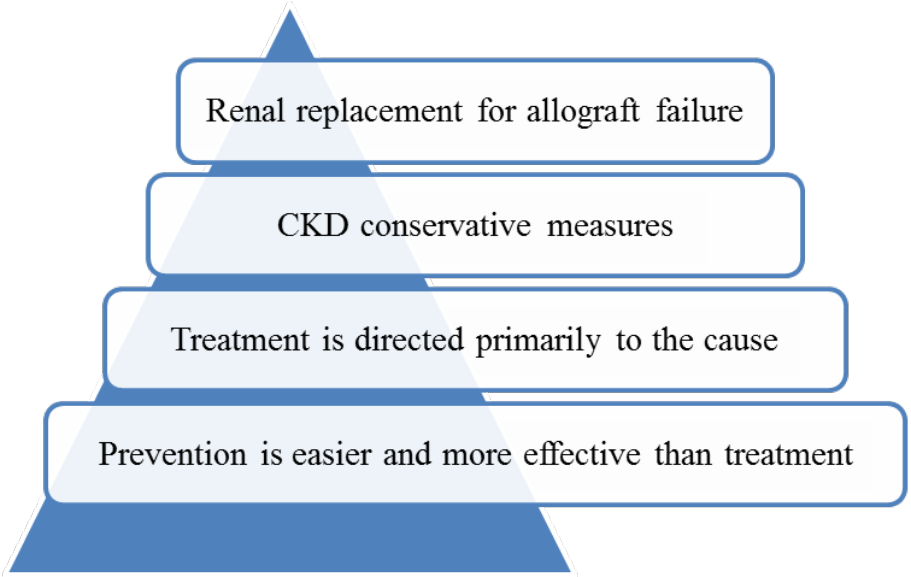
Definition: *It is a condition characterized by progressive loss of renal graft function.*

Renal biopsies show characteristic but nonspecific histopathological changes in the vascular, glomerular and tubulointerstitial compartments of the kidney.

Causes	**Examples**
Immunological causes	T-cell- and antibody-mediated rejection
Drug toxicity	Calcineurin inhibitor toxicity
Infections	CMV, BK Polyoma virus infections, repetitive urinary tract infections with an accompanying pyelonephritis of the graft
Recurrent glomerular disease	Focal segmental glomerulosclerosis, IgA nephropathy, MPGN, anti-GBM disease, HUS or ANCA associated vasculitis
De novo glomerular disease	
Diabetes mellitus	
Arterial hypertension	
Non- compliance to immunosuppressive medications	
Graft senescence	

IgA: immunoglobulin A, MPGN: membranoproliferative glomerulonephritis, GBM: glomerular basement membrane, HUS: hemolyticuremic syndrome, ANCA: antineutrophil cytoplasmic autoantibody

MANAGEMENT:



Kidney allograft biopsy is recommended for all patients with declining kidney function of unclear cause, to detect potentially reversible causes.

Histological evidence of CNI toxicity is an indication for reducing, withdrawing, or replacing the CNI.

For patients with CAI, eGFR >40 ml/min/1.73m2, and urine total protein excretion <500 mg per gram creatinine (or equivalent proteinuria by other measures), we suggest mTORi with or without low dose CNI.

CKD conservative measures: They are the same as patients with native CKD

Renal replacement for allograft failure:

It is the same as patients with ESRD either regular dialysis or renal re transplantation with some issues that are specific to re-transplantation.

Immunosuppression with graft failure:

We recommend that immunosuppressive therapy be continued to avoid immunological sensitization if a living kidney donor is available and there is the prospect of re-transplantation pre-emptively or within one year of starting dialysis. We suggest that maintenance immunosuppression may be reduced in these cases

We suggest that, for failed grafts kept in situ, minimal immunosuppression may be required to prevent a chronic inflammatory state unless there are immunosuppression-related complications and an anticipated delay in re-transplantation.

We recommend that all immunosuppression apart from steroids be stopped immediately after transplant nephrectomy, with subsequent gradual withdrawal of steroids.

Surgical issues in the management of the failing renal transplant:

Widely accepted indications for graft nephrectomy include:

- Localizing symptoms (pain, infection, bleeding) that are resistant to medical therapy in a failed graft
- To create space for retransplantation
- To enable complete withdrawal of immunosuppression
- Risk of graft rupture
- Graft malignancy

Special considerations for re-transplantation:

Contra-indications to re-transplantation are the same as for initial transplantation. But, there are some issues that are specific to re-transplantation:

Recurrent disease:
A number of systemic primary diseases recur following renal transplantation. As a general principle, recurrent disease in a first transplant makes further recurrence following re-transplantation more likely.

The most commonly encountered recurrent glomerular disease is focal segmental glomerulosclerosis with a reported incidence of up to 30% in primary transplants, increasing to nearly 100% in retransplants where there has been recurrence in the initial transplant.

BK nephropathy:
It does not constitute a contraindication to retransplantation, but preferably avoiding highly potent immunosuppressive regimens.

Non- compliance to immunosuppressive medications:
It is not an absolute contraindication for re-transplantation, but the risk of non- compliance to immunosuppressive medications in subsequent transplantation is high.

Malignancies and PTLD:
Appropriate therapy, waiting times and/or modified immunosuppressives protocols will be needed

12. INFECTIONS IN KIDNEY TRANSPLANT RECIPIENTS

URINARY TRACT INFECTION

We recommend that all KTRs receive education regarding general measures for prevention of UTI (urogenital hygiene, adequate fluid intake and voiding habits) and that asepsis is emphasized for patients requiring CIC

We recommend chemoprophylaxis for UTI in all KTRs for the first six months using Trimethoprim-Sulfamethoxazole. Nitrofurantoin is the suggested alternative for those with allergy to SMX/TMP

We recommend that urine cultures be obtained for all KTRs with suggestive symptoms and/or with acute graft dysfunction

UTI *is a frequent and potentially important complication of kidney transplantation. The use of antibiotic prophylaxis can reduce the risk of UTI. UTI may cause signs and symptoms of cystitis (dysuria, frequency, urgency and suprapubic pain) or pyelonephritis (fever, loin pain, anorexia, vomiting). Immunosuppression can mask the symptoms of UTI. Elevated creatinine associated with fever, high CRP and leukocytosis are suggestive of pyelonephritis. Pyelonephritis may cause bacteremia, graft failure, sepsis and death.*

PNEUMOCYSTIS JIROVECII PNEUMONIA

Pneumocystis jirovecii is an opportunistic pathogen causing life threatening pneumonia in immunocompromized patients. It is diagnosed by bronchial alveolar lavage or lung biopsy

We recommend that all KTRs receive prophylaxis with SMX-TMP for 6 months after transplantation and for 6 weeks during and after treatment of acute rejection with T cell depleting antibodies.

Recommended treatment consists of SMX-TMP for 2-3weeks, corticosteroids for 5 days then tapered to complete 3 weeks and decreasing the dose of immunosuppressive drugs

Suggested alternatives in case of allergy to SMX-TMP include Pentamidine (prophylactic monthly inhalation <300mg> in patients older than 5 years, IV for treatment), Dapsone (2mg/kg/day), Atovaquone and Clindamycin+pyrimethamine

CANDIDA PROPHYLAXIS

Oral and oesophageal candida prophylaxis with oral clotrimazole or Nystatin is recommended for 3-6 months after transplantation.

Fluconazole is effective but systemically absorbed and interacts with CNIs (enzyme inhibitor)

TUBERCULOSIS

Kidney transplant recipients with latent TB have a high risk of developing clinical TB after transplantation and are therefore good candidates for chemoprophylaxis with isoniazide for 9 months (but it may affect drug level of CNI and mTORi)

Suggested treatment consists of Rifampicin +fluoroquinolone + isoniazide + Ethambutol + pyrazinamide for two months then fluoroquinolone and isoniazide for 12 months

Rifampicin is a strong enzyme inducer so doses of CNIs and MTORi need to be increased

HIV

Screening for HIV infection is recommended for all KTRs. Antiretroviral therapy must be given in HIV patients undergoing kidney transplantation.

HEPATITIS C VIRUS RECOMMENDATIONS

- **HCV-infected KTRs be treated only when the benefits of treatment clearly outweigh the risk of allograft rejection due to interferon-based therapy (e.g. fibrosing cholestatic hepatitis, life-threatening vasculitis).**
- **Monotherapy with standard interferon for HCV-infected KTRs in whom the benefits of antiviral treatment clearly outweigh the risks.**
- **Posttranssplant therapy of HCV +ve KTRs with viral load by PCR using direct antiviral agents according to age-related guidelines for these agents**
- **All conventional current induction and maintenance immunosuppressive regimens can be used in HCV infected patients.**
- **Measure ALT in HCV-infected patients monthly for the first 6 months and every 3–6 months, thereafter.**
- **Perform imaging annually to look for cirrhosis and hepatocellular carcinoma.**
- **Test HCV-infected patients at least every 3–6 months for proteinuria.**
- **For patients who develop new onset proteinuria (either urine protein/creatinine ratio >1 or 24-hour urine protein >1 g on two or more occasions), perform an allograft biopsy with immunofluorescence and electron microscopy.**
- **Patients with HCV associated glomerulopathy not receive interferon.**

HBV

Booster vaccination is recommended for HBsAg –ve KTRs with HBsAb <10mIU/mL

Prophylaxis is required for HBsAg positive KTRs

Lamivudine for 6-12 months starting at the time of kidney transplantation. Resistance should be treated with tenofovir or adefovir

Tenofovir (decrease the developing of drug resistance and less renal toxicity)

Entecavir in case of resistance to tenofovir and lamivudine

Monitoring:

- HBV DNA and ALT level every 3 months for efficacy of drugs
- Ultrasound and alpha feto protein in patients with initial liver cirrhosis

Interferon therapy should be avoided in HBV infected KTRs

EBSTEIN-BARR VIRUS AND PTLD RECOMMENDATIONS

- **Monitor high-risk (donor EBV seropositive/recipient seronegative) KTRs for EBV by NAT:** once in the first week after transplantation; monthly for the first 3–6 months; every 3 months until the end of the first year; and after treatment for acute rejection.
  Potential risks for developing PTLD include young age at presentation; An EBV-negative KTR from an EBV-positive donor and multiple episodes of acute rejection requiring aggressive immunosuppressive therapy.
- Diagnosis is suggested by an increase viral titre by NAT. The diagnosis of PTLD usually requires histological and immunoflurosence examination of a tissue.
- **EBV-seronegative patients with an increasing EBV load should have immunosuppressive medication reduced.**
- **Patients with EBV disease, including PTLD, should have a reduction or cessation of of immunosuppressive medication.**

HERPES SIMPLEX VIRUS 1, 2 AND VARICELLA ZOSTER VIRUS RECOMMENDATIONS:

- **KTRs who develop a superficial HSV 1, 2 infection be treated with an appropriate oral antiviral agent (e.g. acyclovir, valacyclovir, or famciclovir) until all lesions have resolved.**
- **KTRs with systemic HSV 1, 2 infection be treated with intravenous acyclovir and a reduction in immunosuppression.**
  Intravenous acyclovir continue until the patient has a clinical response, then switch to an appropriate oral antiviral agent (e.g. acyclovir, valacyclovir, or famciclovir) to complete a total treatment duration of 14–21 days.
- Prophylactic oral antiviral agent for KTRs experiencing frequent recurrences of HSV 1,2 infection.
- **Primary VZV infection (chicken pox) in KTRs be treated with either intravenous or oral acyclovir or valacyclovir; and a temporary reduction in amount of immunosuppression.**
  Treatment be continued at least until all lesions have scabbed.
- **Uncomplicated herpes zoster (shingles) be treated with oral acyclovir or valacyclovir, at least until all lesions have scabbed.**
- **Disseminated or invasive herpes zoster be treated with intravenous acyclovir and a temporary reduction in the amount of immunosuppression, at least until all lesions have scabbed.**
- **Prevention of primary varicella zoster be instituted in varicella-susceptible patients after exposure to individuals with active varicella zoster infection:**
  Varicella zoster immunoglobulin (or intravenous immunoglobulin) within 96 hours of exposure; if immunoglobulin is not available or more than 96 h have passed, up to a maximuim 10 days after exposure, a 7-day course of oral acyclovir OR for a total course of 3 weeks according to Canadian guidelines.
- **Patients on the waiting list who are VZV IgG negative should be vaccinated prior to transplantation.**

CMV

We recommend CMV risk stratification for all KTRs based on CMV serology; IgG:

- **High risk = Donor positive / Recipient negative (D+R-)**
- **Intermediate risk = Recipient positive (D+R+ or D-R+)**
- **Low risk = Both donor and recipient negative (D-R-)**
- In patients with borderline or indeterminate CMV serology results, the assignment of risk status should assume the higher possible risk:
  - *Borderline donor serology should be considered positive*
  - *Borderline recipient serology should be considered positive if donor is negative and negative if donor is positive*

The use of T-cell depleting antibodies for induction or treatment of rejection, calcineurin inhibitors, the presence of rejection and other viral infections are also risk factors for CMV disease

Measurement of CMV IgM is not routinely recommended due to potential for false positivity

When CMV disease is suspected and when monitoring for preemptive therapy, CMV PCR is recommended

For low risk cases, we recommend no routine prophylaxis provided leukodepleted or CMV negative blood products are used. Serology should be checked after one year.

Prophylaxis for 3 months (100 days), starting maximum day 3 posttransplantation is recommended for high risk cases and suggested for intermediate risk cases.

Prophylaxis for six weeks following T-cell depleting therapy for rejection is recommended for both intermediate and high risk cases.

Extended prophylaxis (6 months or 200 days) may be used for high risk cases.

We suggest monitoring PCR monthly starting at the end of prophylaxis up to 6 months posttransplant when 3 months of prophylaxis are used in high risk cases.

Preemptive strategy, with regular testing with PCR for 6 months and initiating therapy in asymptomatic patients when viral load is detected, may be used in intermediate, but not high risk, cases.

We recommend testing for serology and PCR at one year for all intermediate and high risk cases.

We recommend the use of oral valganciclovir for prophylaxis. The use of aciclovir and valaciclovir should be restricted to situations where ganciclovir/valganciclovir cannot be used.

Recommendations for treatment:

- **All patients with serious (including most patients with tissue invasive) CMV disease should be treated with intravenous ganciclovir.**
- IVIG may be used together with ganciclovir in severe and life-threatening cases
- CMV disease that is not serious (e.g. episodes that are associated with mild clinical symptoms, preemptive cases) may be treated with either intravenous ganciclovir or oral valganciclovir.
- Continue therapy until CMV is no longer detectable by PCR or pp65 antigenemia.
- Consider reducing immunosuppressive medication in life-threatening CMV disease and CMV disease that persists in the face of treatment, until CMV disease has resolved.
- Monitor graft function closely during CMV disease.

BK POLYOMA VIRUS recommendations

Monitoring

- Screening all KTRs for BKV at least monthly for the first 3–6 months; then every 3 months until the end of the first year; whenever there is an unexplained rise in serum creatinine; and after treatment for acute rejection.
- Continue screening for 12 months from the last detectable viral load
- KTRs should be screened for BK viral load with quantitative plasma NAT (suggested); or by performing urine microscopy for decoy cells or by urine PCR.
- A first positive test should be verified within 1-2 weeks by quantitative plasma NAT and a detectable NAT should be repeated after 1 week to assess the rate of rise in viral load.
- Reducing immunosuppressive medications (particularly withdrawing the antimetabolite) when BKV plasma NAT is persistently greater than 10 000 copies/mL (1^{07} copies/L)
- If increasing viral load and/or creatinine, perform renal biopsy (if not done already) which could be stained by SV40 or by electron microscopy. Two cores containing medullary tissue should be ideally examined
- IVIG infusion may be warranted for patients with concurrent rejection.

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

<u>If viral load is between 1000 and 5000 copies/mL:</u>
-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.
-Monitor BK viral load q2 weeks or monthly if stable.

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

<u>If viral load continues to increase and patient is still on MMF:</u>
-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 BPAR)

<u>If viral load continues to increase and patient is not on MMF:</u>
reduce CNI by 25-50%:
-Target cyclosporine trough levels of 50-100 ng/mL or tacrolimus trough level of 3-4 ng/mL.
-Add leflunomide, if not added already.
-Repeat BK viral load q2 weeks.

<u>If viral load continues to rise despite stopping MMF, reducing the CNI and adding leflunomide:</u>
-Stop CNI and ADD sirolimus.
-Repeat BK viral load q2 weeks.

Treating biopsy-proven BKV nephropathy

- 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.

Treatment of BKV nephropathy by modification of maintenance immunosuppression:

Switching	Decreasing	Discontinuing
-Tacrolimus to CsA (trough 100-150ng/mL) -Mycophenolate to AZA (max 3mg/kg/day) -Tacrolimus to mTORi (trough level <6ng/mL) -MMF to leflunomide	-Tacrolimus (trough levels <6ng/mL) -Mycophenolate (600 mg/m2/day MMF or 360mg/m2/day MPS) -Cyclosporine (trough levels around 100)	Tacrolimus or MMF (maintain or switch to dual therapy) with steroids plus either a CNI, an mTORi or MMF

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)
- In addition to ensuring adequate immunosuppression, consider discontinuing leflunomide once the BK viremia has resolved and the 0patient is stable.

13. MALIGNANCY IN KIDNEY TRANSPLANT RECIPIENTS

We recommend that all KTRs be regularly and actively monitored for the development of malignancy, particularly lymphoproliferative disorders and skin malignancy

We recommend that KTRs, especially those who have fair skin, live in high sun-exposure climates, or have a history of skin cancer minimize life-long sun exposure and use appropriate ultraviolet light blocking agents

We suggest that patients with a history of skin or lip cancer, or premalignant lesions, be referred to and followed by a qualified health professional with experience in diagnosing and treating skin cancer.

We suggest to obtain hepatic ultrasound and alpha feto-protein every 12 months in patients with compensated cirrhosis.

We recommend that reconsideration of immunosuppression be considered a part of the management of KTRs with malignant or premalignant conditions.
Reduced quality of life from graft loss must be balanced against the potential for prolonging survival by reducing immunosuppression.

Viral infections associated with (increased risk of) malignancy
***HBV and HCV**: Liver*
***Human T-cell lymphotropic virus type 1** Non-Hodgkin lymphoma*
***Human Herpes virus 8** Kaposi sarcoma*
***EBV** Nasopharynx, Non-Hodgkin lymphoma, Hodgkin lymphoma*
***HPV** Tongue, mouth, tonsil, anus, vagina, cervix, penis*

For patients with PTLD or Kaposi sarcoma, we suggest using mTORi along with a reduction in overall immunosuppression.

It is recommended that patients with PTLD wait for at least one year after achieving disease remission prior to consideration of re-transplantation.

Patients with SCC must have all current lesions removed before re-transplantation and be clear of metastatic disease. However there is no requirement to wait for a disease-free interval prior to re-transplantation.

Kaposi's sarcoma often resolves on withdrawal of immunosuppressive therapy but the rate of recurrence after re-transplantation is high. Regression on treatment with sirolimus provides the option for re-transplantation with sirolimus as primary immunosuppressive therapy but outcomes using this approach are uncertain, as is the appropriate interval prior to re-transplantation.