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RESEARCH ARTICLE

Pearls in Paediatrics Renal Transplantation. A Discussion on Debatable Issues

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Abstract

Renal transplantation is the treatment of first choice for paediatrics chronic kidney disease. Owing to the tremendous impact of chronic kidney disease on general health and growth of the children which would not be alleviated by other modalities of renal replacement therapy, kidney transplantation must be provided for all the patients regardless to the underlying aetiology of renal disease. The commonest cause of chronic kidney disease is congenital anomaly of urinary tract. It instigates pre-transplant corrective interventions to ascertain successful transplantation. Herein, we elucidate the different aspects of paediatrics kidney transplantations, elaborating on unique preparatory measures considered in the context of congenital bladder dysfunction and obstructive uropathy. Furthermore, we discussed peculiar issues relevant to the surgical procedure for implanting renal allograft for paediatrics recipients. Moreover, we addressed contentious issues pertinent to post transplantation varied immune suppression protocols and its related potential complications. Lastly, we formulated an alleged protocol for complicated cases of paediatrics kidney transplantation.

Keywords: Paediatrics Transplantation, Bladder Dysfunction, Immune Suppression Protocol.

1. Introduction

Chronic kidney disease incidence amount to 11.9 patients per million age related people (pmarp)in paediatrics age group in European registry.Similarly, incidence of paediatrics patients on renal replacement therapy was variable, hence it reaches to eighteen pmarp in New Zealand, dwindled down to fifteen pmarp in USA and less than 4 pmarp in Russia.Kidney transplantation is the therapeutic modality of choice for paediatrics end stage renal failure patients, as it is associated with superior long-term survival and particularly, adequate regaining of normal general growth and recovery of renal bone disease[1]. In this article we are discussing contentious issues related to various aspects of paediatrics renal transplantation.

2. Preparation and Pre-Transplant Work up

It involvestwo parts:

2.1 General Part

Which consists of the commonly requested laboratory tests to assess the readiness of a potential candidate for the transplant operation and the immune suppression status post operatively.

These tests include:

1. Complete blood count looking for anaemia of any kind.
2. Liver function test, to exclude liver diseases.
3. Calcium, phosphate, and Parathyroid hormone for assessment of renal bone disease and parathyroid disorders contingent to chronic kidney disease.
4. Radiology investigation
5. Chest Xray to exclude presence of chronic infective process. Abdomen ultrasound study to screen for urological abnormalities. Importantly, virology screening is pivotal for stratifying post-transplant management and suitability of potential donor. The concerned viruses are: Cytomegalo virus CMV, Epstein-Barr virus EBV, Hepatitis C and B viruses, herpes simplex virus, Varicella zoster virus and HIV.The discrepancy of virology status between the potential donor and recipient

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impacts the procedure and entail preparation to undermine risk of transmission and infection post transplantation.

6. Tissue typing and cross match: For both the potential donor and recipient including HLA -A, HLA-B and HLA-DR to categorize level of mismatch.

For the potential recipient calculated reaction frequency CRF tests the sensitivity of the recipient to different common HLA antigens to frame the degree of HLA sensitization. Flow cytometry cross match and direct cross match to detect the donor specific antibodies DSAs and stratify its intensity [2].

2.2 Specific Part

As the common aetiology of chronic kidney disease is congenital anomaly of urinary tract and kidney{CAUTK}, its pivotal to address this issue thoroughly. In another study, bladder dysfunction was shown to constitute 20-30% of patients with ESRD[3].

Indications for further urological work up in potential paediatric kidney transplant candidates [4]:

1. Recurrent urinary tract infection
2. Hydronephrosis and or hydroureter.
3. Urinary tract symptoms linked to bladder emptying abnormalities.
4. Most importantly, the patients with vesico-ureteric reflux VUR associated reflux nephropathy and chronic pyelonephritis. Similarly, posterior urethral valve PUV associated chronic obstructive nephropathy.

2.3 Investigations Recommended for Evaluating Bladder Function in this Category of Candidates

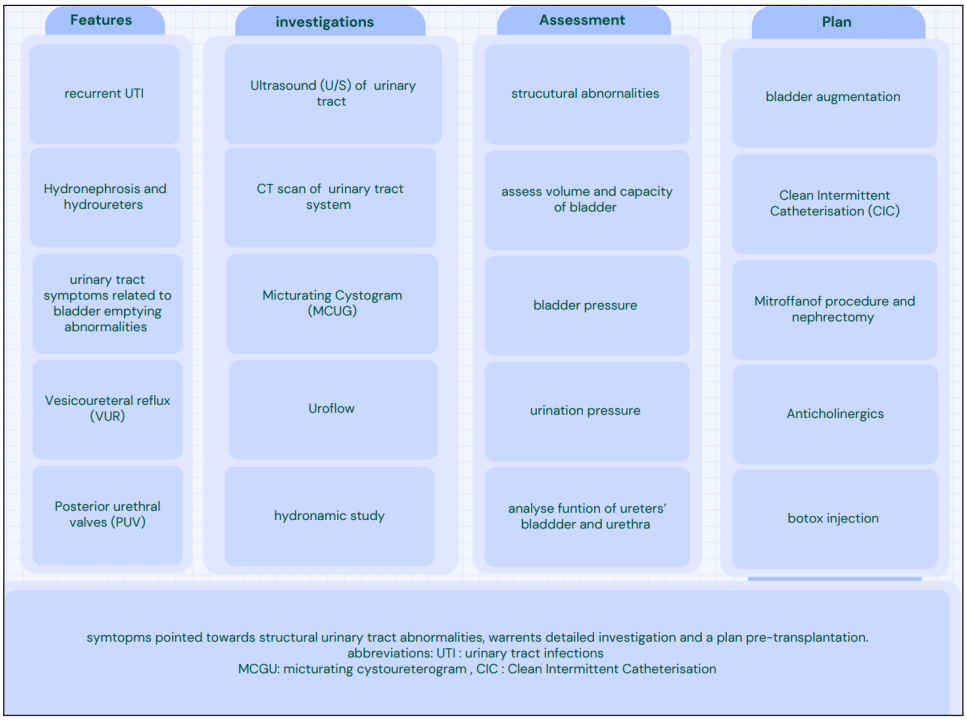
1. Micturating cystourethrogram MCUG:

A contrast material is installed in the bladder via a catheter, then a dynamic imaging study performed during urination. It is a diagnostic study for VUR, PUV, other urethral lesions and post void residual urine volume.

2. Uroflow and urodynamic study

2.4 For Bladder Function Assessment. This Study Addresses the Following Integral Bladder Related Issues [5]

1. Volume and capacity of the bladder.
2. Bladder pressure in relation to bladder volume.
3. Urination function and related pressure.
4. Analyse the integrated function of ureter, bladder, and urethra.



3. Management of VUR in Potential Kidney Transplant Candidate

Prevalence of VUR in general population is 17.4%. VUR associated ESRF incidence is 14.8 Per million patients per year. VUR leads to CKD via inflicting reflux nephropathy which is progressing to ESRD [6]. Assessment of bladder function is mandatory in patients with history of VUR. It is conceptualized that VUR post transplantation is commonly predisposing factor for urinary tract infection when it's associated with voiding abnormalities.VUR with no significant

post-transplant bladder outflow obstruction dose not portend an increased risk of consequent post-transplant urinary tract infection, impaired allograft function, rejection, or hypertension. Hence urodynamic study is a principal pre-transplant investigation for candidate patient with VUR [7].

4. The Urodynamic Study Features Consistent with Outflow Obstruction are [7]

1. High bladder pressure
2. Small volume capacity of less than 100 ml
3. Impaired bladder outflow.
4. Soaring micturition pressure of more than 100 cm water.

In the context of VUR, these findings are indicative of significant obstructed or spastic bladder. On the contrary, a non-functioning bladder with non-elevated filling pressure concoct with better outcome with no increased adverse events. The management of spastic, low-capacity bladder is bladder augmentation.

5. Augmentation of Bladder Pre-Transplantation [8]

It's a surgical procedure aimed at correcting congenitally anomalous bladder with low capacity, by creating a low-pressure pouch to accommodate the urine volume adequately. The emptying of this pouch is performed either by Valsalva manoeuvre or clean intermittent catheterization CIC. The most common surgical technique adopted for bladder augmentation is utilization of the ureters, particularly the dilated ureters resultant from VUR. The other option is enterocystoplasty which involves enlarging the bladder with a bowel segment {either ilium or sigmoid}, ilium is preferred because it's a large, long organ.

The other VUR related complication is dilated ureters. In grade III-IV VUR disease the ureters are dilated and tortuous predisposing to recurrent febrile urinary tract infections with increasing morbidity and mortality in the context of immune suppressed status post transplantation. It is a contentious issue as treatment is debatable, varied with different trends, experience, and centre-based practice in outlining the pre-transplant and post-transplant management. Generally, to anatomically restore the dilated dysfunctional vesico-ureteric junction sphincter, three approaches are commonly followed[9]:

1. Surgical: open re-implantation of the ureter: the most successful procedure, 95-99% success rate, performed via an intravesical approach [Politano and Leadbetter] and extra-vesical Lich-Gregoir approach. Open surgical procedure is more efficient than laparoscopic and robotic assistant surgical procedure
2. Endoscopic: minor invasive procedure involves injecting bulking material in the periureteric tissues plain via a cystoscope through either hydrodistension implantation technique or sub-ureteral trans urethral injection technique with resultant alteration of the angle and fixation of the intra vesical ureter. Success rate range between 70-90%.
3. Utilization of the distended ureters for creation of reservoir in bladder augmentation.

6. Posterior Urethral Valve PUV

It's a congenital membrane that persist in the posterior urethra obstructing the bladder outflow[10].

PUV is a major cause of ESRD in paediatric age group. Its commonly leading to renal dysplasia and bladder dysfunction which is constantly persist after ablation of the PUV. Hence, bladder function assessment via ultrasound study, micturating cystourethrography and urodynamic study is indicated as outlined earlier. Bladder assessment is an integral part of pre-transplant preparation, as it was reported to be abnormal in 50 % of patients with PUV. Several patterns of bladder function abnormalities are identified in this context, which is collectively called valve bladder syndrome.

7. Valve Bladder Syndrome VBS[11]

Persistent bladder dysfunction after correction of PUV was reported in 33% of cases in one study. This residual bladder dysfunctionis collectively tagged as VBS. VBS encompasses different phenotypes streamlined by urodynamic study and micturating cystourethrogram into:

1. Spastic bladder: Owing to bladder outflow obstruction incurred by PUV, bladder wall developed muscular hypertrophy with extensive fibrosis which would reflect high filling pressure and diminished capacity.
2. VUR: secondary to elevated intravesical pressure,vesico-ureteric sphincter's closure fails, with consequent VUR, which constantly persist after correction of PUV.
3. Recurrent urinary tract infection UTI.
4. Over-stretched non-myogenic, flaccid, and persistently distended low-pressure bladder
5. Hyperactive bladder.

The management stratified according to the relevant VBS phenotype.

7.1 Spastic Bladder

1. Anticholinergics: To reduce the overactivity and muscular hypercontractility, anticholinergics such as such as oxybutinin, tolterodin, darifenacin and solifenacine are administered.
2. In patients who failed to respond to anticholinergics with resultant persistent highfilling pressure, muscular hyperactivity and VUR, intra-vesical botulinum toxin [Botox] injection is the principle second line therapy. By inhibiting neuro-muscular junction, the intravesical injection of Botox relaxes bladder detrusors muscles and hence minimizes vesical pressure and spasticity, boosting bladder compliance.
3. Bladder augmentation BA: as described earlier, BA is an alternative therapeutic option for patients with non-compliant spastic bladders who did not improve on anticholinergics and Botox injection.BA procedure enlarges the bladder size and therefore bladder capacity with consequent decreasing intravesical pressure and improving VUR.

7.2 Non-Myogenic Bladder

Clean intermittent catheterization CIC is the manoeuvre of choice for managing non-myogenic bladder failure or any other phenotype of VBS who showed post-void residual bladder urine volume of more than 10 % of total pre- void volume[12].

7.2.1 CIC

CIC is the habitual transient placement of urinary catheter under meticulous clean aseptic condition. It's the standard of care for management of urine retention in the context of distinct categories of bladder dysfunction, such us VBS.

7.3 Urine Retention UR

UR is the persistence of post-void residual PVR urine volume secondary to failure of bladder emptying mechanism. PVR urine volume of less than 100 ml is considered normal, and more than 200 ml is abnormal and consistent with UR. In children, PVR urine of more than 20 ml is diagnostic of UR [13].

The common consequences of persistent urine retention are:

1. Worsening of bladder dysfunction, features incontinence, nocturia, hesitancy, frequency, urgency and VUR.
2. Recurrent and chronic infection might provoke pyelonephritis of both the native and transplanted kidney as well.
3. Stone formation.

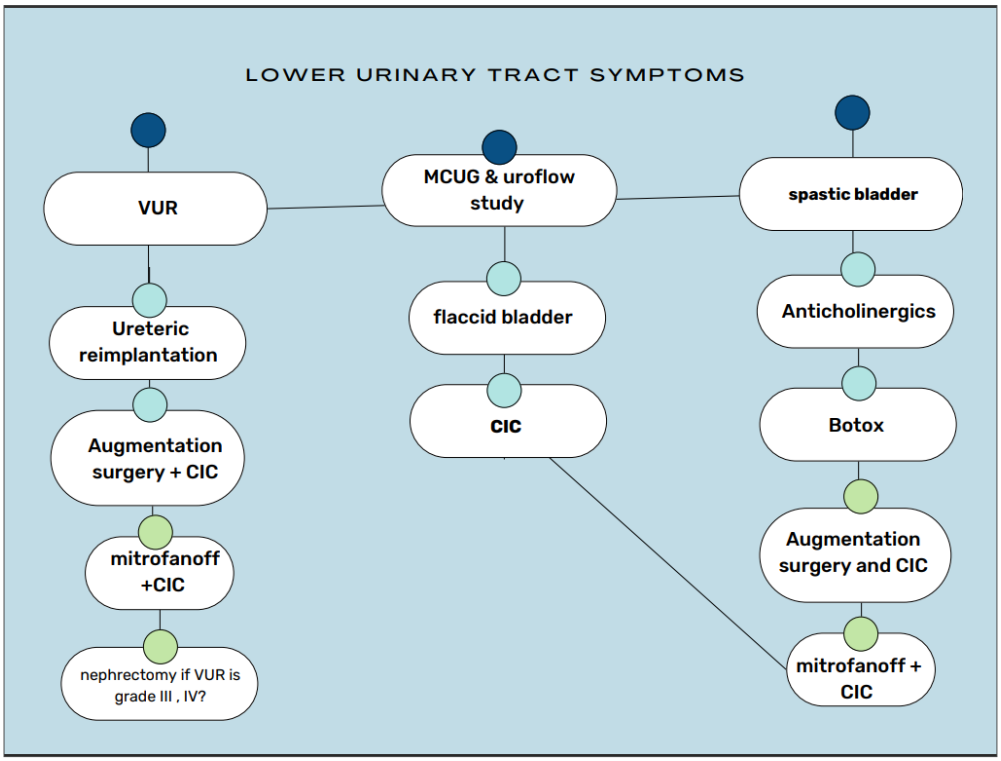


Figure 2. *Assessing patient with urinary tract symptoms via MCUG and uroflow study would basically identify 3 abnormal functioningbladder phenotypes, spastic, flaccid and VUR bladder, each modality is treated differently. Abbreviations: VUR; vesico-ureteric reflux. MCUG; micturating cystourethrogram. CIC; clean intermittent catheterization.*

It was found that CIC is associated with better long term outcome post transplantation.

7.4 Mitrofanoff Procedure {Appendeco Viscicostomy}[14]

It's the creation of a continent catheterizeable channel between the bladder and the skin by utilizing the appendix as a conduit to facilitate emptying of bladder via an external stoma. It's indicated in patients with:

1. Painful catheterization.
2. Urethral stricture or injury.
3. Augmented bladder with significant PVR urine.
4. Atonic flaccid bladder with large volume and low pressure.
5. PUV non corrected or difficult to correct with urethral ablation.

After creating Mitrofanoff stoma, CIC is applied every 4 to 5 hours for proper emptying of the bladder.

It is contraindicated in high pressure bladder dysfunction as its predisposing to VUR. The major complications reported are intestinal obstruction, leakage, and bleeding.

8. Unique Surgical Aspects in Paediatrics' Renal Transplantation [15]

Kidney transplantation is the promising modality of renal replacement therapy for end stage renal disease children.However, certain aspects of transplantation procedure entail specific technical pitfalls, including:

1. Size mismatch of adult donors' kidney and small size recipients' body due to lack of adequate intra-abdomen room for placement of the allograft which necessitate pretransplant nephrectomy to create adequate space, a pre-requisite that increased the cost, inherent surgical complication, and general complications of anephric status.
2. Vascular anastomosis: Owing to the size-mismatched of paediatrics-adult vasculatures, securing a proper anastomosis is pivotal to maintain adequate blood supply to the allograft.
3. Intra-abdomen compartment syndrome associated allograft ischemia and thrombosis is critical in this context.
4. Corrective surgical procedure for the bladder depending on its abnormalities.
5. Bladder draining manoeuvre with CIC, Mitrofanoff conduit creation.
6. Nephrectomy of native kidneys.

9. Indications for Native Kidney Nephrectomy NKN, in Paediatrics Renal Transplantation [16]

NKN is a contentious issue in paediatrics transplantation. It is instituted when the native kidney poses a potential threat to the transplanted kidney or the recipient life. In a single centre study, proteinuria was the most common indication for NKN. However, NKN was allegedly indicated in the following conditions:

1. Massive proteinuria, of more than 40 mg/mm/hour. As nephrotic syndrome and hypoalbuminemia harbinger detrimental potential consequences for the allograft and the patient such as: Allograft thrombosis, malnutrition, hypovolemia induced allograft dysfunction and post-transplant wound healing failure which is commonly predisposed to via loss of anti-coagulants along with albuminuria and dysregulated compensating hepatic over production of coagulation factors. On the other hand, proteinuria induced consequent hypalbuminaemia presaged hypovolemic status, impairing the perfusion of renal allograft which the patient is inherently predisposed to, owing to donor kidney and recipient size discrepancy. Moreover, hypoalbuminemia is commonly associated with growth retardation of the children. NKN was reportedly linked to improved general outcome of patients with nephrotic syndrome.
2. Uncontrolled hypertension. It was revealed in several studies, that NKN is associated with a better control of intractable hypertension.
3. Recurrent urinary tract infection and complicating urosepsis. As the immune suppressed status post transplantation confer a heightened risk of complicated septicaemia particularly when occurred in the context of CAKUT.
4. Renal stone disease.
5. Hydronephrosis and hydroureter.
6. Polyuria: of more than 2.5 ml/kg/hour. It entails a critical situation post transplantation as volume depletion and difficulty in managing fluid replacement might be resultant in hypovolemia associated allograft dysfunction and allograft vessels thrombosis.
7. Cystic renal disease: NKN performed to create a room for the renal allograft.
8. Malignancy or pre-malignant lesion.

Nevertheless, NKN is not without complications to the child, as bilateral nephrectomy results in anuric status and dependence on dialysis with challenging water and electrolytes control. Furthermore, post-transplant fluid management would be exceedingly difficult to accomplish. On the other hand, multiple surgeries herald potentially increasing risk status for anaesthesia related complications, infection, and thromboembolism.

10. Unilateral, Staged Nephrectomy and Simultaneous NKN and Transplantation [17]

To minimize the inherent risk of complications related to bilateral nephrectomy, unilateral nephrectomy and staged nephrectomy procedures were advocated. In unilateral nephrectomy, significant reduction of proteinuria and urine output were reported. Nevertheless, a comparable outcome results were identified between staged and simultaneous nephrectomy/ transplantation procedure in another single cohort study.

10.1 Implantation of Adult Donor Allograft

Several approaches were practiced for implanting a large adult size renal allograft into a small size child recipient abdominal cavity. Each approach is inherently denoting different advantageous aspects, meanwhile, integrating unique drawbacks.

10.2 Surgical Approaches [18]

10.2.1 Intra-Peritoneal Implantation

In which the allograft is implanted intra-peritoneally via a midline incision. The complications and hurdles commonly reported with this approach are:

a. Scars and adhesions of previous surgeries.

b. Intra-abdominal hypertension and abdominal compartmental syndrome, attributed to size mismatch that increased the intra-abdominal pressure.

c. Consequent to that, detrimental reduction in allograft blood supply might supervene. This complication was reported with an incidence of 7.6% in one study.

d. Similarly, secondary to intra-abdominal hypertension, other intra-abdominal organs ischemia might be concurred. An incidence of 5.3% was highlighted.

e. However, the most reportedly encountered complications are the gastrointestinal tract related complications. Intestinal obstruction was increasing reported as well as incisional hernia and volvulus.

f. Intra-peritoneal allograft implantation is associated with increasing complications linked to freely intra-peritoneal movement of the allograft resulting in an increasing risk of twisting and obstruction of relevant blood vessels and transplanted ureter.

10.2.2 Extra-Peritoneal Approach

Extra-peritoneal implantation of allograft precludes the common complications inherent to intra-peritoneal implantation. However, this approach is necessitating nephrectomy to create a space for the donor allograft. Several complications are reported in the context of this approach, linked to prolonged surgery, anaesthesia, and fluid management as detailed earlier.Allograft biopsy is easier with extra-peritoneal implantation.

A novel modified approach was advocated for extra-peritoneal implantation to avoid nephrectomy by performing en-block native liver and renal auto-transplantation.

The selection of allograft implantation site intra-peritoneally vs extra-peritoneally is entirely patient and centre -protocol dependent pertinent to several parameters including body weight of the recipient, history of previous abdominal surgeries, intension to preserve peritoneal cavity for peritoneal dialysis.

10.2.3 Vascular Anastomosis

Owing to vascular size discrepancy, paediatrics kidney transplantation is associated with increasing risk of post operative vascular complications, hence peculiar surgical manoeuvres, including avoidance of vascular redundance, tension-free interrupted anastomosis to aorta and IVC for allograft renal artery and allograft renal vein respectively, avoidance of vascular overlapping of allograft vein and artery are commonly advisable for minimizing these adverse outcomes.[19]

10.2.4 Anti-Coagulant Administration Post Transplantation

It is advocated to administer anti-coagulants post operatively to decrease the risk of vascular thrombosis. It revealed superior outcome in comparison to no-anticoagulant administration. [20]

11. HLA Effect on Kidney Transplantation Outcome

Major histocompatibility complex antigen is the main determinant for success of kidney transplantation, as it modulates the immune system and response to

allograft. The more donor/recipient HLA mismatch, the more sensitization would result against the kidney allograft. This mismatch would negatively impact the allograft and patient survival. HLA mismatch is a potential stimulus for production of donor specific antibodies DSAs against the foreign mismatched HLA antigen, which would be recognized as ***un-acceptable antigens***. These un-acceptable antigens deter potential second transplantation as it could result in rebound of DSAs with detrimental consequences of acute and chronic antibody mediated rejection ABMR. Hence it was highlighted in several registry that the risk of allograft failure is increasing steadily in proportion to severity of mismatch ranging from 6% with one mismatch to 76% with six mismatches. Certain HLA mismatched antigens are linked to robust DSAs production and adverse allograft outcome, such as HLA A, B, DR which are highly polymorphic and DQ. In Paediatric transplantation, it is of paramount importance to consider best HLA matching to minimize the potential sensitization and production of DSAs, as children are potentially contemplated for second and third kidney transplantations [21].

11.1 Immune Suppressant Protocol for Kidney Transplantation [22]

Immune suppressants protocol in paediatrics transplantation pertained to two concerning aspects post transplantation. First, is to overcome the risk of rejection by proper inhibition of immune system. Secondly, is to prevent over-immune suppression related side effects, particularly, opportunistic infection, diabetes mellitus, growth retardation, malignancy, and bone disease. Stratification of immune suppression protocol is entirely dependent on patient's risk factors, these are:

1. HLA incompatibility.
2. PRA more than 0
3. Presence of donor specific antibodies DSAs.
4. Previous transplantation.
5. Background aetiology of chronic kidney disease, immunologically mediated versus CAKUT.
6. Virology status of the patient. Particularly CMV, EBV and BK polyoma virus.

11.2 Steroid use in Paediatrics Renal Transplantation

Corticosteroid is the corner stone of immune suppression protocol. As its inhibiting IL 1, 2, 3, and IL6. However, its use is associated with myriad of inherent complications, particularly its effect on growth, bone complications and provoking of diabetes mellitus. Hence, it's indicative in immunologically high-risk recipients and avoided in other patients. A joint multidisciplinary decision is advocated on best immunosuppression protocol on patient based.

11.2.1 TWIST Protocol

For low-risk patients an early steroid withdrawal protocol is considered as follows:

1. Methylprednisolone 10 mg/kg not more than 1 gram on day 0.
2. Prednisolone sixty on day one to be tapered to 0 on day 5.
3. Tacrolimus of 0.15 mg/Kg body weight twice a day not to exceed 10 Mg daily dose. Trough tacrolimus level is 8-12 ng/ml during the first 2 months and then 5-8 ng/ml from 3rd month onwards.
4. Mycophenolate Mofetil MMF 600 mg/mm for 2 weeks post operatively and then 300 mg/mm thereafter.

For induction Therapy: Anti-IL2 receptor monoclonal antibody, basiliximab,is administered at a dose of 10 to 20 mg on day 0 and day 4 depending on body weight of the patient. However,other literatures recommend rATG over basiliximab in a dose of 1.5 mg/kg/day on day 0 to be repeated to a maximum dose of 4.5-7.5 mg/kg depend on immunologic risk assessment. Studies revealed no benefit of higher doses {more than 7.5 mg/kg} with regards to occurrence of first documented rejection.

There is no consensus on best treatment protocol for induction and maintenance therapy. General outline depends on local experience and risk stratification of the patient. Hence, other centres upheld different protocols, recommending continuation of corticosteroid immune suppression with allegedly better long-term outcome with less rejection rate.

11.2.2 PAT-B Protocol

It involves prednisolone maintenance indefinitely, azathioprine 2 mg/kg instead of MMF and tacrolimus with basiliximab induction.

11.3 Kidney Donor Complication

Post donation complications stemmed from reduction of renal mass post-nephrectomy. These complications include chronic kidney disease with reduction of eGFR below 60 ml/min, proteinuria, and hypertension. Furthermore, incidence of diabetes mellitus was increased as well. The incidence of pre-eclampsia

was higher in kidney donors pregnant than in counter part non-donors pregnant with an incidence of 4-10%. Its advisable to better control of relevant risk factors for progression of chronic kidney disease such as diabetes, hypertension, and obesity [23].

11.4 Challenges for Adolescent's Allograft Recipients

It was reported that the most common reason {53%} for allograft failure in adolescent recipients is non-compliance.

Several studies highlighted the transition period from childhood to adulthood as the critical period during which psychological factors influence the decision and intensions of the patients when care givers are changed from paediatrics to adult transplant physicians.It is recommended to have a transition team including transplant nurse, psychologist, paediatrics, and adult transplant physician for the patient during this period[24].

12. Conclusions

1. Kidney transplant is the best option for chronic kidney disease child.
2. We recommend pre transplant bilateral nephrectomy for patients with persistent bilateral VUR and bilateral hydronephrosis.
3. If there is no bladder obstruction, for transplant candidates with bladder dysfunction, we recommend augmentation procedures for spastic bladder after trial of anticholinergic medication and Botox injection.
4. For all patients with bladder dysfunction who underwent corrective procedure CIC is implemented properly to avoid recurrence of infection and persistence of VUR.
5. Mitrofanoff procedure is recommended for those patients who failed to empty the bladder properly.
6. We recommend unilateral pretransplant nephrectomy for transplant candidate with persistent nephrotic syndrome and or massive proteinuria. To avoid the potential complications of bilateral nephrectomy.
7. We inclined to assess each kidney transplant candidate as per his merits with regards to implantation of the allograft in the intra-peritoneal versus extraperitoneal spaces.
8. It is indicated to have the best HLA matched donor for paediatrics recipients, to avoid the development of potential DSAs.
9. Its recommended to stratify the immunosuppression protocol for each patient according to risk/ benefit scale with an emphasis its on minimizing side effects and improving growth of the children.
10. For adolescent age group transplanted recipients, we recommend having a transition team that would critically assess each patient circumstances to ensure smooth transit of transplant care.

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