International Journal of Trend in Scientific Research and Development (IJTSRD)
Volume: 3 | Issue: 2 | Jan-Feb 2019 Available Online: www.ijtsrd.com e-ISSN: 2456 - 6470

Renal Transplantation in Children

Sangeeta Dewangan

B.SC. Dialysis Technology, Pt. J.N.M. Medical College Raipur, Chhattisgarh, India

ABSTRACT

The goal of a successful transplant has beep accomplished in more than three fourths of the children with end-stage kidney disease treated in a special program undertaken at Los Angeles Childrens Hospital some years ago. In general, rehabilitation (both physical and psychologic) and growth have been highly satisfactory, the latter especially when transplantation was carried out before puberty.

Although the number of children with end-stage renal disease (ESRD) in need for renal transplantation is small compared with adults, the problem associated with renal transplant in children are numerous, varied, and often peculiar. Pre-emptive transplantation has recently been growing in popularity as it avoids many of the associated long-term complications of ESRD and dialysis. Changes in immunosuppression to more potent agents over the years will have affected transplant outcome; there is also evidence that tacrolimus is more effective than cyclosporine. This review will discuss the short- and long-term complications such as acute and chronic rejection, hypertension, infections, and malignancies as well as factors related to long-term graft function.

Chronic allograft nephropathy is the leading cause of renal allograft loss in pediatric renal transplant recipients. It is likely that it reflects a combination of both immune and nonimmune injury occurring cumulatively over time so that the ultimate solution will rely on several approaches. Transplant and patient survival have shown a steady increase over the years. The major causes of death after transplantation are cardiovascular disease, infection and malignancy. Transplantation in special circumstances such as children with abnormal urinary tracts and children with diseases that have the potential to recur after transplantation will also be discussed in this review. Non-compliance with therapeutic regimen is a difficult problem to deal with and affects patients and families at all ages, but particularly so at adolescence. Growth may be severely impaired in children with ESRD which may result in major consequences on quality of life and self-esteem; a better height attainment at transplantation is recognized as one of the most important factors in final height achievement.

Keywords: *ESRD, children, transplantation*

INTRODUCTION

Kidney transplantation is universally accepted as the therapy of choice for children with end-stage renal disease (ESRD). two-thirds of pediatric patients with ESRD ultimately receive a kidney transplant.

Successful transplantation in children and adolescents not only ameliorates uremic symptoms, but also allows for significant improvement of delayed skeletal growth, sexual maturation, cognitive performance, and psych social functioning. For pediatric patients of all ages, transplantation results in better survival than dialysis.

Five-year survival rates in transplant patients range from 94% to 97%, while in dialyzed patients the survival rate ranges from 75% to 87%.

Although incidence rates for glomerular diseases have remained steady in the pediatric population, the incidence rates for patients with congenital, hereditary, and cystic diseases have trended upward over the past 20 years.

In contrast to adults, ESRD caused by diabetes mellitus or hypertension is rare in children. Incidence of treated end-stage renal disease in pediatric patients[a] according to primary disease.

Primary Renal Disease	Incidence (%)
Glomerulonephritis (GN)	29.8
Focal segmental glomerulosclerosis	10.0
Membranoproliferative GN	2.5
Rapidly progressive GN	2.1
IgA nephropathy	1.6
Goodpasture syndrome	0.7
Membranous nephropathy	0.5
Other proliferative GN	1.5
Unspecified GN	10.3
Cystic, hereditary, and congenital disease	26.0
Renal hypoplasia, dysplasia	8.9
Congenital obstructive uropathy	6.7
Alport syndrome, other familial disease	2.7
Autosomal dominant polycystic disease	2.0
Autosomal recessive polycystic disease	1.0
Prune belly syndrome	1.1
Congenital nephrotic syndrome	1.2
Medullary cystic disease (nephronophthisis)	1.1
Cystinosis	0.7
Other	0.3
Interstitial nephritis, pyelonephritis	9.1
Nephrolithiasis, obstruction, gout	3.2
Chronic interstitial nephritis	2.0
Chronic pyelonephritis, reflux nephropathy	2.7
Nephropathy caused by other agents	0.9
Secondary GN, vasculitis	8.9
Systemic lupus erythematosus	4.6
Hemolytic uremic syndrome	1.9
Henoch-Schonlein purpura	0.9
Wegener granulomatosis	0.7

Timing of Transplantation
Renal transplantation should be considered when renal replacement therapy is indicated.

In children, dialysis may be required before transplantation to optimize nutritional and metabolic conditions, to achieve an appropriate size in small children, or to keep a patient stable until a suitable donor is available.

Many centers want a recipient to weigh at least **8 to 10 kg**, both to minimize the risk for vascular thrombosis and to accommodate an adult-sized kidney. In infants with ESRD, a target weight of 10 kg may not be achieved until 12 to 24 months of age.

Preemptive transplantation (i.e., transplantation without prior dialysis) accounts for 24% of all pediatric renal transplantations.

PROGNOSTIC FACTORS INFLUENCING GRAFT SURVIVAL
The following factors are important determinants of the improving graft survival reported in pediatric patients.

Long-term renal function is a particularly important consideration in pediatric renal transplantation because of its impact on post-transplant skeletal growth.

Donor Source
Short- and long-term graft and patient survival rates are better in recipients of *living donor transplants* in all pediatric age groups.

Younger transplant recipients benefit the most from living donor transplantation and enjoy a 20% to 30% better graft survival rate 5 years after transplantation.

Shorter cold ischemia time, better human leukocyte antigen (HLA) matches, lower acute rejection rates, and better preoperative preparation help to account for the better outcome in recipients of living donor kidneys.

Recipient Age
In the past, there has been a trend for younger children, especially those younger than 2 years of age, to have lower graft survival rates than older children, especially with deceased donor kidneys.

Now that trend seems to be reversed. Some studies even suggest that infant recipients of adult kidneys with immediate function may have the longest half-lives of any type of kidney transplant.

The rates were 92% for infants younger than 1 year, 81% for children 1 to 5 years old, and 80% for children 6 to 10 years old.

The results for deceased donor recipients were also better in this age group than in adults generally. Recipients 1 to 5 years of age have a 5-year graft survival of 68% and recipients 6 to 10 years of age have a 5-year rate of 72%, the best of all age groups.

Donor Age
For all deceased donor recipients, kidneys from donors aged 11 to 17 years provide optimal graft survival and function.

This group is followed next by donors ages 18 to 34, 6 to 10, and then 35 to 49 years. Grafts from donors younger than 5 years old fare more poorly, and grafts from patients older than 50 years fare most poorly.

Although transplanted kidneys grow in size with the growth of the recipient, transplantation with deceased donor kidneys from donors younger than age 6 years is associated with markedly decreased graft survival.

Human Leukocyte Antigen Matching in Children
In pediatric transplantation, most living donor transplants come from parents. Long-term graft survival is best when the donor is an HLA-identical sibling.

When considering transplants from HLA haplotype-identical sibling donors, studies suggest that there is improved outcome when donor and recipient share 'noninherited maternal antigens', as distinct from 'noninherited paternal antigens'.

With regard to deceased donor transplantation, improved outcome has been reported with the sharing of both HLA-B and HLA-DR antigens.

Presensitization
Repeated blood transfusions expose the recipient to a wide range of HLA antigens and may result in sensitization to these antigens, leading to higher rates of rejection and graft failures.

The graft failure rate increases by up to 40% for recipients with more than five blood transfusions before transplantation, as compared with those who had fewer transfusions.

Immunologic Factors
Immunologic parameters in younger children are different from those in adults and older children.

Such differences include higher numbers of T and B cells, higher CD4+:CD8+ T-cell ratio, and increased blastogenic responses. These differences may account for increased immune responsiveness to HLA antigens and may be partly responsible for the higher rates of rejection that had been observed in children.

Standard evaluation of pediatric kidney transplant candidates
History and physical examination
Laboratory tests -Hematology (complete blood count with platelets and differential)

Coagulation (prothrombin time, partial thromboplastin time, thrombin time) Chemistry (serum electrolytes, blood urea nitrogen, creatinine, liver function tests, lipid panel,serum electrophoresis, parathyroid hormone.

Urine (urinalysis, urine culture, 24 hour urine for protein)

Blood bank/immunology (ABO type, hepatitis profile, human immunodeficiency virus, HLA type, antileukocyte antibody screening.

Virology
Cytomegalovirus
Epstein-Barr virus
Herpes simplex virus
Varicella zoster virus
Measles, mumps, rubella titers

Radiology
Vesicourethrogram or (VCUG)
voiding cystourethrogram
Chest x-ray
Bone age
Electroencephalogram
Consultations
Social worker
Dentists
Neurologist
Psychologist
Nutritionist
Cardiologist

Vaccines
(2 months prior to transplantation)
Pneumococcal
Hepatitis A / B
Purified protein derivative
Varicella

For urological problem
PV USG
MCU
Urodynamic study
Urinalysis, urine culture sensitivity
Bladder repair or nephrectomy may be required before transplantation

PERIOPERATIVE MANAGEMENT OF THE PEDIATRIC RENAL TRANSPLANT RECIPIENT
Preparation for Transplantation
For living donor transplants some programs commence immunosuppression in the week prior to the transplant date.

A final cross-match is performed within 1 week of transplantation, and the patient is evaluated clinically to ensure medical stability.

Laboratory tests obtained at admission permit detection of metabolic abnormalities that require correction by dialysis.

Aggressive fluid removal is discouraged in the immediate preoperative period to reduce the risk for delayed graft function.

Intraoperative Management
Methylprednisolone sodium succinate (Solu-Medrol), 10 mg/kg, is given intravenously at the beginning of the operation. Close attention is paid to blood pressure and hydration status in an attempt to reduce the incidence of *DGF*.

Typically, a central venous catheter is inserted to monitor the central venous pressure (CVP) throughout the operation.

To achieve adequate renal perfusion, a **CVP of 12 to 15 cm H_2O** should be achieved before removal of the vascular clamps; a higher CVP may be desirable in the case of a small infant receiving an adult-sized kidney.

Dopamine is usually started in the operating room at 2 to 3 µg/kg per minute and increased as required and is continued for 24 to 48 hours postoperatively. It is used to facilitate diuresis and perhaps to effect renal vasodilatation.

The *mean arterial blood pressure* is kept above 65 to 70 mm Hg by adequate hydration with a crystalloid solution or 5% albumin and, if necessary, the use of dopamine at higher doses.

Blood transfusion with packed red blood cells may be required in very small recipients because the hemoglobin may drop as a result of sequestration of about 150 to 250 mL of blood in the transplanted kidney. Mannitol and furosemide may be given before removal of the vascular clamps to facilitate diuresis. Urine volume is replaced immediately with 0.5% normal saline.

Occasionally, an intra-arterial vasodilator, such as verapamil, is used to overcome vasospasm that may impair renal perfusion.

Postoperative Management
Because of the small size of young children, fluid management must be fastidious. Urine output should be replaced on a cc for cc basis with *0.45% or 0.9% normal saline continued for 24 to 48 hours*.

Insensible water losses are replaced with a dextrose-containing crystalloid. *Potassium replacement* may be required. Dextrose is not added to the replacement solution and is only used as part of the insensible water loss replacement solution.

Withholding dextrose in the urine replacement solutions helps to prevent post-transplant hyperglycemia and osmotic diuresis.

The lack of concentrating ability of the newly transplanted kidney accounts for an obligatory high urine output that may be observed in the first few post-transplantation days.

As the kidney function improves and the serum creatinine levels fall close to normal values, urinary concentrating ability recovers, and urine output decreases from several liters per day to amounts that begin to match daily fluid intake.

At this time, urine output replacement can be stopped, and daily fluid intake is usually set to provide about 150% to 200% of the normal daily maintenance needs, preferably administered orally.

Postoperative orders for pediatric kidney transplant recipients
Nursing
Vital signs every 30 min for 4 hr, then every hour for 24 hr
Central venous pressure and urine otput every hour for 24hr
Urine for glucose; abdominal girth; peripheral pulses; and nasogastric pH every 4 hr
Guaiac stool daily; turn, cough, and suction (as needed)

Laboratory
Serum electrolytes, hematology, coagulation, and arterial blood gas immediately postoperative and at 4 hr postoperative
Serum electrolytes, calcium, and phosphorus every 4 hr for 24 hr
Daily electrolytes and hematoloty; coagulation and liver function tests twice weekly; cyclosporine levels 3 days week

Fluids
1 ml IV for 1 ml urine each hour (5% dextrose in water/45% normal saline with 10 mEq sodium bicarbonate/L if urine

output < 8 ml/kg/hr; the glucose is changed to 1% dextrose in water if > 8 ml/kg/hr)

Medications
Trimethoprim sulfa (2-4 mg/kg/day)
Antacid (1 ml/dose for < 2 yr old, 2 ml for 2-5 yr, and 3 ml for 5-10 yr)
Nystatin 4 times/day, pain medication, and immunosuppression

Radiology
Chest radiograph immediately postoperative and on postoperative day 1
Stent study on postoperative day 6

Post operative prophylaxis:
Protocols for post-transplant **antibiotic prophylaxis** in children vary from center to center. Most centers use an intravenous cephalosporin for the first 48 hours to reduce infection from graft contamination and the transplant incision.

The use of nightly trimethoprim-sulfamethoxazole for the first 3 to 6 months serves as prophylaxis against *Pneumocystis carinii pneumonia* and urinary tract infections.

Prophylactic oral miconazole (nystatin) minimizes oral and gastrointestinal *fungal infections*. *CMV prophylaxis* has to be given.

Children who have undergone *splenectomy* should be immunized with *pneumococcal vaccine* and should receive postoperative prophylaxis for both gram-positive and gram-negative organisms, both of which may cause overwhelming sepsis.

Immunosuppressive protocol for pediatric kidney transplantation
Pretransplant (1 wk in living donor recipients only)
- Prednisone: 0.5 mg/kg daily (minimum dose = 20 mg/d)
- MMF: 600 mg/m^2/dose b. i. d. + Famotidine: 1 mg/kg/dose b. i. d. (maximum = 40 mg b. i. d.: other H_2 blockers, except cimetidine, or H_+ pump blockers may be used)

Pretransplant (6-24 hr)
- Daclizumab: 1 mg/kg in 50 mL of normal saline IV over 30 min
- MMF: 600 mg/m^2 PO within 6 hr

Intraoperatively
- Solumedrol: 10 mg/kg IV at the beginning of surgery (maximum dose of 1 g)

Immediate postoperative period
- Solumedrol: 0.5 mg/kg/d IV (minimum dose = 20mg/day)[a]
- MMF: 600 mg/m^2/dose IV q 12 hr[a]

Cyclosporine: 10-15 mg/kg/d PO divided b.i.d. For children who weigh lessthan 10 kg or are younger than 6 yr of age, give 400-500 mg/m^2/d divided t.i.d.[b] The dose is adjusted to achieve trough levels of 250-350 ng/mL and/or C2 levels of 1200-1500 ng/mL.

OR

Tacrolimus 0.15-0.2 mg/kg/day PO divided b. i. d. to achieve levels of 8-12 ng/ml.[b] + Famotidine or H_2 blocker

Maintenance therapy
- Daclizumab: 1 mg/kg at 2, 4, 6, and 8 wk after transplantation
- Prednisone: Dose tapering is started 2 wk after transplantation and continued to reach a maintenance dose 0.07-0.1 mg/kg/d by 3-4 months.
- MMF: 600 mg/kg/dose PO b.i.d. with cyclosporine, 300-400 mg/kg/dose PO b.i.d. with tacrolimus[c]

Cyclosporine/tacrolimus: Dose is adjusted to achieve the desired trough levels

H_2, histamine-2;MMF, mycophenolatemofetil. The drug is given orally when the patient tolerates oral intake.

Cyclosporine/tacrolimus is started once urine output has been established and the serum creatinine level is below 2.5-3 mg/dL or less than 50% of its baseline value before transplantation. The dose can be spread to a three-times-daily schedule if gastrointestinal symptoms develop early.

Guidelines for drug dose tapering in pediatric renal transplant recipients
1. Cyclosporine/Tacrolimus
Minimal or no change in the first 4 weeks to allow for faster tapering of prednisone.

Dose reduction should not exceed 10%-20%. Cyclosporine/Tacrolimus and prednisone doses should not be lowered on the same day (risk ofprecipitating an acute rejection).

Serum creatinine and cyclosporine/tacrolimus levels should be checked 2-3 days after each changeand before the next change is made. (The same guidelines are applied to patients treated with tacrolimus.)

2. Prednisone
Start tapering the dose 2-3 weeks after transplantation if stable and cyclosporine /tacrolimus level is within the desired range.

Initial dose tapering is by 2.5 mg each time, about 10% (may reduce by 5 mg if total dose is >2 mg/kg).Once a 10-mg dose is reached, dose reduction is by 1 mg each time.

Longer periods of time should elapse before further tapering at the lower dose range. Cyclosporine/Tacrolimus and prednisone doses should not be lowered on the same day.

Serum creatinine and cyclosporine/tacrolimus levels should be checked 2-3 days after each change and before the next change is made.

3. Mycophenolate mofetil
Dose reduction is only indicated if hematologic or gastrointestinal side effects develop.

Dose reduction is done in 30%-50% increments.It can be safely withheld for a few days up to 2-3 weeks for severe side effects.

Post transplantation complications: 1. Primary non function of allograft
Prolonged cold ischemia times
Hyperacute rejection
Acute Tubular Necrosis

2. Surgical complications
Lymphocoele
Hematoma
Urinary leak
Vesicoureteric Junction obstruction

3. Vascular
Renal vein thrombosis
Renal artery thrombosis

4. Acute Rejection
Acute rejection is seen in first 3 months. Rejection in the first 3 weeks is called as accelerated rejection.

Serum creatinine has to be monitored.

Differential diagnosis of increased serum creatinine include dehydration, urinary obstruction and acute rejection. Acute rejection is treated with intravenous methyl prednisolone 10-15 mg/kg for 3 days.

5. Infections:
The spectrum of infections and their presentation may differ somewhat between children and adults and the following section focuses on these differences.

Infection in the immunocompromised child remains the major cause of morbidity and mortality after transplantation, and is the most frequent reason for posttransplant hospitalization.

6. Hypertension:
Hypertension is commonly observed. Pain is an important cause of hypertension in the immediate postoperative period, and adequate analgesia may be all that is required to control blood pressure.

Hypertension is rarely aggressively corrected in the immediate postoperative period to avoid sudden swings in blood pressure that may impair renal perfusion. Long term hypertension is generally due to cyclosporine or steroid use and is treated with sodium restriction, calcium channel blockers or beta adrenergic blockers.

7. Hematological complications
- *Anemia* is usually due to MMF or azathioprine
- *Aplastic Anemia* is due infection with Parvovirus B 19 or CMV infection.
- *Hemolytic Anemia* due to hemolytic uremic syndrome may occur
- *Erythrocytosis* may be due to use of Neoral or FK 506.
- *Neutropenia* or thrombocytopenia may be due to MMF or viral infections.

8. Metabolic complications
Hypomagnesemia, hypophosphatemia, hyperkalemia, hypercalcemia and renal tubular acidosis.

9. RECURRENCE OF DISEASE
Several diseases are known to recur in the allograft and adversely affect long-term outcome.

Oxalosis:
Children with oxalosis have a high rate of recurrence leading some to believe they should not be transplanted. There are, however, two other alternatives.

The first is performing a LD kidney transplant followed by aggressive medical management aimed at increasing the solubility of urinary calcium oxalate.

The second is a combined kidney liver transplant, wherein the liver transplant cures the metabolic disease preventing recurrence in the kidney. The latter option is the treatment of choice for infants where the liver enzymatic defect is likely to be complete.

10. Delayed acute rejection:
occurs 6-12 months after transplantation and is usually due to noncompliance or viral infection.

11. Chronic Allograft nephropathy:
Important causes include
- Chronic rejection
- Calcineurin inhibitor nephrotoxicity
- Hypertension
- Hyperlipidemia
- CMV
- Recurrent native disease
- Denovo glomerulonephritis

12. Malignancy:
Post renal transplantation lymphoproliferative disease that occurs in EBV negative recipients of EBV positive donors is common in children.

13. Growth Retardation:
Retarded skeletal growth is a constant feature in children with chronic renal failure and ESRD. The severity of growth retardation is directly related to the age of onset of renal failure; the earlier the onset, the more severe.

Renal osteodystrophy, metabolic acidosis, electrolyte disturbances, anemia, protein and calorie malnutrition, delayed sexual maturation, and accumulation of uremic toxins have all been implicated in the development of growth retardation.

Growth retardation is typically assessed by:
- Standard deviation score (SDS) or
- Height deficit score (also known as the Z score). These measure the patient's height compared with that of unaffected children of similar age.

Determinants of Post transplant Growth
Growth improves after transplantation; however, full catch-up growth is not realized in most patients. The following factors have a major influence on post-transplantation growth.

Age
Children younger than 6 years of age have the lowest standard deviation scores before transplantation, and these exhibit the best improvement in their SDS after transplantation. Two years after transplantation, infants younger than 1 year of age have an improvement in their SDS by 1 full standard deviation (SD), compared with an improvement of only 0.5 SD for those between 2 and 5 years of age, and 0.1 SD in those between the ages of 6 and 12 years.

Children older than 12 years of age tend to have minimal or no growth after transplantation. Older children occasionally continue to grow into puberty; however, the growth spurt experienced by most growing children at this age may be blunted or lost.

The fact that youngest children benefit the most in statural growth from early transplantation provides a strong argument for expedited transplantation in an attempt to optimize and perhaps normalize stature.

In addition, earlier transplantation allows less time for growth failure while receiving dialysis and therefore a lesser requirement for catch-up growth.

Corticosteroid Dose

The precise mechanism by which steroids impair skeletal growth is unknown. They may reduce the release of growth hormone, reduce insulin-like growth factor (IGF) activity, directly impair growth cartilage, decrease calcium absorption, or increase renal phosphate wasting.

Strategies to improve growth include the use of lower daily doses of steroids, the use of alternate-day dosing, or dose tapering to complete withdrawal.

Conversion to alternate-day dosing should be considered in selected, stable patients in whom compliance can be assured.

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Ideally, steroids are withdrawn completely. In tacrolimus-based immunosuppressive regimens, withdrawal of steroids within the first 6 months has been successfully performed in more than 70% of patients.

The effect of this approach on growth has been remarkable, with improvement in the SDS at 2 years after transplantation in children younger than 13 years of 3.6 SD in the withdrawn group, as compared with 1.5 SD in the non-withdrawn group.

Growth Hormone

The use of recombinant human growth hormone (rhGH) in pediatric renal transplant recipients significantly improves growth velocity and SDS.

Growth hormone therapy is generally started in prepubertal children at least 1 year after transplantation and continued until catch-up growth is achieved or until puberty ensues.

Cyclosporine levels may fall after initiation of rhGH therapy, and the dose should be increased by 10% to 15%.

Allograft Function

A GFR of less than 60 mL per minute per 1.73 m^2 is associated with poor growth and low IGF levels; optimal growth occurs with a GFR greater than 90mL per minute per 1.73 m^2.

Differences between pediatric and adult renal transplantation

- Higher CD4:CD8 ratio
- Higher number of B and T cells
- Rejection rates are more
- Longer anastomosis times
- Longer ischemia times
- Higher rate of early graft rejection
- Higher rate of delayed graft function and vascular anastomoses
- Increased Dose of cyclosporine required due to increased hepatic metabolism
- Growth retardation is an important factor
- Steroid has to be tapered early
- Urological problems require bladder augmentation

CONCLUSION

Transplantation is currently the best option for children with ESRD. Surgery and modern immunosuppression have demonstrated excellent results, provided the children are managed in a pediatric center with experience in the management of all aspects of pediatric renal transplantation. However, such a therapeutic option is not accessible to all children in the world because of political, economical, and cultural issues in developing countries.

Conclusions We pediatric urologists have in the past been very worried about the future of the very small patients with ESRD, most of whom were under our personal follow up or treatment since they were fetuses. The possibility of offering a kidney transplantation to small and very young children without a higher percentage of postoperative surgical complications and with good or even better results than in older patients is a very promising concept.

A surgically corrected serious urological abnormality has not been in our experience a limitation for a living related kidney transplantation. Many previous or simultaneous reconstructive operations will be an obligatory part of the treatment. These results should encourage pediatric urologists and nephrologists to perform these type of procedures in young patients more frequently when a live related donor is available.

Although pediatric kidney transplantation is active in some parts of many developing countries, it is still inactive in many others and mostly relying on living donors. The lacking deceased programs in most of these countries is one of the main issues to be addressed to adequately respond to organ shortage.

In conclusion, transplantation is currently the best option for children with ESRD. Although improvement in immunosuppression demonstrated excellent results and has led to greater 1-year graft survival rates, chronic graft loss remains relatively unchanged and opportunistic infectious complications remain a problem.