Update Article

Chronic Kidney Disease in Children: An Indian Perspective

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Chronic renal failure (CRF) is an insidious and irreversible condition that eventually progresses to end stage renal failure. It is an important cause of morbidity and mortality in children worldwide. The disease process is better termed as chronic kidney disease (CKD), in order to encompass the entire spectrum and severity of renal disease. In the past various terminologies have been used to describe its severity from chronic renal insufficiency to end stage renal disease (ESRD). This classification did not include the 'at risk' population where intervention could modify the outcome. In order to reduce ambiguity and use more objective terms of reference the new name of CKD was introduced. Chronic kidney disease is defined primarily as an abnormality of kidney function or structure as determined by laboratory tests, urinalysis or imaging tests, which have been present for three or more months. Importantly, the classification system describes the stages according to level of estimated glomerular filtration rate (GFR), not serum creatinine levels. This staging uses various clinical, laboratory and imaging parameters [1] and is depicted in Table1. These stages correspond to the severity of kidney function loss and the prevalence of co-morbidities associated with kidney disease. The identification of low GFR states may allow the implementation of simple measures to prevent worsening. For these reasons, it may be prudent to adopt the system of defining kidney disease according to kidney function, not serum creatinine values. However certain grey areas exist with this classification. The staging takes into consideration normal GFR for a western population. It has been noted that healthy Indians especially on a vegetarian diet have a lower GFR [2]. Secondly, correct interpretation of GFR values in children and adolescents, requires a clear understanding that it varies according to age, gender, and body size. The normal GFR in young adults is 120 to 130 mL/min/1.73 m^2, whereas in infancy it is much lower. Even when corrected for body surface area it increases in relationship to body size up to two years. Kidney disease is characteristically asymptomatic and is often not diagnosed until it is relatively advanced.

Table 1

Stages of chronic kidney disease

Stage	Description	GFR (ml/min/1.73 m^2)
1	Kidney damage with normal or increased GFR	>90
2	Kidney damage with mild decrease GFR	60-89
3	Moderate decrease GFR	30-59
4	Severe decrease GFR	15-29
5	Kidney failure	<15

Magnitude of Problem

The magnitude of CKD varies from one geographical area to another due to genetic and environmental factors. In the absence of a national registry, the exact incidence and burden of CKD in children in India is not known. In our institution with a dedicated pediatric nephrology unit, the patient load of kidney disease in children is approximately 8-10% of total outpatient attendance and 12% of admissions to the pediatric ward. The commonest diagnosis for which children are likely to see a pediatric nephrologist is nephrotic syndrome constituting almost 40% of cases. Keeping in view that almost 10% of them are steroid resistant, they would constitute a large burden of children with CKD. Urinary tract infection (UTI) is another problem commonly associated with renal outflow obstruction or a reflux. A similar morbidity pattern has been reported from a neighbouring country where 65% of children with renal disease had UTI followed by nephrotic syndrome accounting for another 20% [3].

A review of available Indian literature reveals a paucity of information on the etiology of CRF in children,

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hence it is difficult to comment on the burden of CKD in the country. In the absence of any screening guidelines children with CKD Stages 1, 2 and very often Stage 3 may not receive any medical attention. This is substantiated from a study from India of adult patients with a vesicoureteric reflux where 80% patients had CRF at presentation, including 38% with ESRD. A reflux was diagnosed during routine pre-transplant evaluation in 5.5% of all adult ESRD patients [4]. In another series 58% of children with renal failure had ESRD at presentation [5]. A substantial percentage of the pediatric CKD population develops renal insufficiency very early in life but may not receive medical attention. As against this, the data from the North American Pediatric Renal Transplant Co-operative Study (NAPRTCS) reveals that children with Stage 1 constitute 28% and Stage 2 or 3 constitute 70% of children registered for CKD [6].

An understanding of the important causes of CRF in any country is important as it may guide the distribution of limited resources towards its prevention. Thereafter monitoring and management depends on the stage of CKD irrespective of the cause. Thus a sound knowledge of the children likely to develop Stage 5 CKD helps utilise the resources in monitoring these children and directing all intervention programs toward retarding the progression of disease. In a series of 305 children, median age 8 years, presenting with CKD at a tertiary care hospital in India, the cause of renal failure in 75% of cases was obstructive nephropathy, reflux nephropathy or chronic glomerulonephritis [7]. In children presenting at an older age chronic glomerulonephritis is more common [8]. However obstruction and interstitial nephritis form a large percentage of cases. A similar trend has been reported from other developing countries. [9]. As against this, the data from developed countries reveals that besides obstructive uropathy, congenital aplasia/hypoplasia/dysplasia is an important cause for CKD in children [10].

Screening for CKD

The importance of detecting and staging CKD is to follow a rigid approach that is appropriate for children who are at increased risk for developing CKD. This information is important for pediatricians, family physicians, pediatric nephrologists, urologists and other health care providers who have the opportunity to detect CKD in children and adolescents during its early stages. Children at risk for CKD as depicted in Table 2 need close monitoring [11]. Screening of apparently healthy children has been found to be useful in detecting early chronic glomerulonephritis [12]. In Japan where generations of people underwent the school-screening program, the age that a patient develops ESRD has been rising year by year and the number of new ESRD patients starting treatment before 20 years of age is lower. However such a screening program may not be cost effective in India where more children develop CKD due to an obstructive or reflux nephropathy or steroid resistant nephrotic syndrome. An improved awareness of early diagnosis, treatment and subsequent evaluation of a UTI in an infant is probably required. Follow-up of children with antenatal detected renal abnormalities and a simple observation of the urinary stream in a male newborn at birth could aid in the early diagnosis of urinary tract obstruction and vesicoureteric reflux.

Table 2

Children at risk for the developement of CKD

- Family history of renal disease
- Antenatal detected renal anomalies
- Neonatal acute renal failure
- Low birth weight babies
- History of urinary tract infection with reflux
- History of nephritis or nephrotic syndrome
- Lower urinary tract obstruction
- Diabetes
- Autoimmune disease
- Renal rickets
- Hypertension
- Long term use of non steroidal anti inflammatory drugs

Management Plan

Management of children with CKD aims at possible interventions to retard progression of disease and the treatment of co-morbid conditions in the early stages. The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K/DOQI) Clinical Practice Guidelines for Chronic Kidney Disease in Children has proposed an action plan for each stage of CKD [13]. For a child with Stage 1 CKD, treatment of the primary and co-morbid conditions with measures to slow the progression and reduce the cardiovascular disease risk factors are recommended. At Stage 2 and 3 it is important to regularly estimate the rate of progression of CKD while ensuring a constant evaluation and treatment for co-morbid conditions. The glomerular filtration rate in the clinical setting may be estimated by the Shwartz formula (K x height in cms/serum creatinine, where K is the constant and is 0.55 in young children). If local laboratory constants are derived and the height is known, this formula offers accuracy with least mathematical complexity [14]. At Stage 4, preparations for renal replacement therapy are initiated, since by CKD Stage V it is imperative to provide this therapy.

Retard Progression

Early identification of factors with a potential to accelerate the progression of renal disease helps plan

Table 3
Factors hastening the progression of CKD

- Obstruction to the urinary tract
- Ongoing active glomerular disease
- Hypertension
- Proteinuria
- Infections of the urinary tract
- Hyperlipidemia
- Use of nephrotoxic medications

the course of action in a child with CKD. All attempts should be made to determine the aggravating factors for worsening renal functions in any given child [11]. These are enumerated in Table 3. A strict control of blood pressure, measures to reduce proteinuria, control of hyperlipidemia and the use of angiotensin converting enzyme inhibitors (ACEI) are recommended. Benefits of protein restriction are unproven in children. All nephrotoxic medications are best avoided when alternatives are available for *e.g.* in a child with CKD, fever and pain can be treated with paracetamol instead of NSAID's like ibuprofen or nimuselide. It is important to avoid dehydration especially in children with tubulopathies and polyuria. The use of nephrotoxic medications in a setting of sepsis and dehydration has a cumulative nephrotoxic effect. Urosepsis needs early diagnosis and treatment. Ongoing glomerular injury is most often immune mediated and needs treatment with immunosuppressants.

The most effective early intervention seems to be the use of ACEI. Ramipril in a dose of 0.1-0.2 mg/kg/day has been shown to lower blood pressure significantly, decrease proteinuria and significantly decelerate GFR with similar relative efficacy in patients with hypo/dysplastic nephropathies and glomerulopathies [15]. The blood pressure lowering and antiproteinuric effects are greatest in severely hypertensive and proteinuric children. Long-term studies indicate a renoprotective effect of ACEI in patients with sequelae after hemolytic uremic syndrome as well [16].

Treatment of Co-morbid Conditions

Anemia, renal osteodystrophy and acidosis are often the presenting features and have a variety of deleterious consequences.

Anemia may be the only presentation in children with CKD and in India where the incidence of iron deficiency anemia and other hemoglobinopathies is common, it is not unusual to miss the diagnosis of CKD. It is associated with lower quality of life across the spectrum of stages of CKD [17]. In a series of children presenting with chronic renal failure the mean hemoglobin at presentation was 7.2 ±2.6g/dL [5].

Renal osteodystrophy : Altered calcium phosphorus and vitamin D metabolism occurs early in CKD and all patients with GFR of less than 60 ml/min/1.72m^2 need to have this disturbance monitored. This aspect is more relevant in children with tubulointerstitial disease where bone disease may manifests at higher GFR. Monitoring of blood levels of calcium, phosphate and alkaline phosphatase is useful. Bone alkaline phosphatase is nonspecific but shows good co-relation with bone histology and is more readily available, cheaper and reliable as against the parathormone (PTH) assays which may be subjected to sampling errors. A dynamic bone disease is less common in children. Besides growth retardation and the development of bony deformities vascular abnormalities are also severe in children who are on maintenance dialysis and are related to abnormal calcium-phosphorus metabolism. Therefore it is imperative to use phosphate binders and an active form of vitamin D regularly along with dietary modifications to reduce the intake of phosphates during the conservative management of children with CKD.

Acidosis develops early in children with CKD due to obstructive or tubulointerstitial renal disease. Serum bicarbonate should be measured three to six monthly in early CKD and monthly once the disease advances. Serum bicarbonate levels should be maintained at or above 22 mEq/L. Sodium bicarbonate tablet containing 4 mEq base per tablet of 325 mg is readily available in India and is a cheap preparation for regular use in children with acidosis.

Nutrition: Children with CKD are considered at high risk for protein-energy malnutrition. In the Indian scenario, where malnutrition is widely prevalent in the general population, the problem becomes even more intense. It is recommended that the daily requirements of calories and proteins of high biological values must be met with. Children on dialysis, especially chronic ambulatory peritoneal dialysis (CAPD) need a higher protein intake. This is difficult to ensure when the child may have anorexia superimposed onto the catabolic response caused by the uremic state. Dietary supplements of energy and protein may be required. If oral nutrition is inadequate, children may require tube feeding. In developed countries this is ensured via a percutaneous enterogastrostomy stoma used for overnight infusion of feeds.

Additional problems of growth retardation and cardiac dysfunction need to be addressed early. One child with CKD can drain the entire family financially, psychologically and emotionally. The impact of the disease on the child, the siblings and the family need to be studied in India and a support system developed.

Vaccination

Children born with renal insufficiency need to be given all routine immunization including the hepatitis, varicella and pneumococcal vaccines. These are of special importance in a child who is to be initiated on dialysis or considered for a renal transplant. All patients being considered for dialysis should receive the hepatitis B vaccine. A rapid schedule of 0,1,2 (months) with a booster at 12 months may be used. It is routine to use a double dose, as seroconversion is poor when the GFR is low. Once on dialysis the patients should be routinely screened for HBsAg. It is not unusual to get a transient positive status within a few days of immunisation and this should be interpreted with caution. A two dose schedule for the varicella vaccine is recommended to all children on conservative management for renal failure, some may require a third dose if antibody levels are low prior to a transplant. The new conjugate pneumococcal vaccine is now available in India. It is more efficacious and safe in children less than two years of age. This vaccine is now routinely recommended for all children with renal insufficiency in developed countries. The Hib vaccine is strongly recommended for children with reduced renal function. For babies born with renal failure, the aim is to complete all immunization by 17 months, so as to enable them to be ready for a possible transplant. No transplant should be considered for three months if any of the live vaccines have been administered.

Renal Replacement Therapy

Once a child develops CKD Stage V, some form of renal replacement therapy (RRT) is required. The choice is limited to a chronic dialysis or renal transplant. A pre-emptive transplant is possibly the best option. Besides providing a good renal replacement therapy it ensures better growth and does not drain the family resources. The facilities for providing renal replacement therapy to children with CKD Stage 5 are grossly inadequate in India. The lack of a health insurance scheme or a national ESRD program makes RRT beyond the reach of the majority. The options for RRT other than a transplant include chronic hemodialysis (HD) or CAPD. For successful dialysis appropriate sizes of catheters, tubings, dialysers, small volume dialysate bags, etc, are required. These are now available in our country. The cost of peritoneal dialysis is two times higher than haemodialysis if infrastructure and manpower costs are not taken into consideration. The goal of treatment in children with ESRD is renal transplantation.

Children on long-term hemodialysis show subnormal growth, poor quality of life and delayed sexual maturation. Hemodialysis is performed, 2-3 days a week, in the hospital as a daycare procedure with each session lasting for 3-4 hours. In developed countries home nocturnal haemodialysis is becoming a feasible option [18]. In comparison to adults, the procedure of hemodialysis is technically more difficult in children and requires close monitoring to prevent complications. Dedicated pediatric hemodialysis units with skilled nursing and technical staff are necessary to provide safe and effective hemodialysis for children. The high cost of hemodialysis in relation to per capita income is a constraint for long-term dialysis and the maintenance of a satisfactory vascular access is a major technical problem faced by pediatric hemodialysis units. In a series from India, from a total of 33 children with ESRD enrolled for maintenance HD, 25 either died due to complications related to inadequate dialysis or opted out due to financial constraints [19]. It is felt that more paediatrics hemodialysis units with trained personnel are required for meeting the unique needs of children.

CAPD provides near steady-state biochemical control with no risk of dysequilibrium syndrome, minimal need for dietary and fluid restrictions and freedom from repeated dialysis needle puncture. CAPD exchanges are carried out 4-5 times a day with very meticulous attention for maintaining asepsis. Parents need to be explained and trained about the techniques for performing exchanges and trouble shooting. Despite adequate precautions, such patients are at significant risk for peritonitis. Smaller dialysate bags are not freely available in our country resulting in wastage of dialysis fluid and increased cost with the use of larger bags. However it is a viable option for a successful bridge between ESRD and renal transplantation [20].

Renal transplantation is undoubtedly the best option. A number of centers are undertaking pediatric transplant in India. The percentage of children receiving a transplant as against those requiring one is dismal. In the absence of a transplant registry or a cadaver transplant program, children are most likely to receive a kidney from a live related donor, more often the mother. Graft survival ranges from 73%-88% at one year and 71%-86% at three years [21-23].

What we need in India today are more trained pediatric nephrologists and pediatric nephrology units. Studies in developed countries have shown that children with CKD cared for by pediatric nephrologists fare better in the long run than those managed at adult nephrology units [24]. In a situation of limited resources it may be more cost effective to direct them towards preventive nephrology. There in lies a greater role for the pediatric nephrologists to detect and treat children at risk for CKD. This may reduce the burden of young adults requiring RRT. In the words of James Joyce, one of the most significant writers of the 20th century: "*I am tomorrow,*

or some future day, what I establish today. I am today what I established yesterday or some previous day…". How we care for the child today, will have an impact on his well-being tomorrow when he has grown into an adult.

Conflicts of Interest

None identified

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