INTRODUCTION

Chronic Kidney Disease

Chronic kidney disease (CKD) is a worldwide public health problem, with adverse outcomes of kidney failure, cardiovascular disease, and premature death.[1] Knowledge of the epidemiology of varying stages of CKD is important for implementing effective measures for slowing the progression of the disease in at risk individuals and allocating enough health care resources for facilitating access to renal replacement modalities. These aspects are of special concern in low-income and middle-income countries, where the clinical and socioeconomic consequences of the disease are expected to be higher.[2, 3]

Definition and Stages of CKD:

A simple definition and classification of CKD is necessary for international development and implementation of clinical practice guidelines. Historically, the terms chronic renal failure (CRF) and chronic renal insufficiency (CRI) have been used to describe varying degrees of renal dysfunction. The term chronic kidney disease is now the accepted terminology for persistent renal dysfunction in the adult and pediatric nephrology communities around the globe. The use of the term CKD allows for both consistency when discussing degrees of injury and also highlights the fact that renal dysfunction occurs along a continuum rather than as discrete steps of declining function.[4]

In 2002, the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) published detailed clinical practice guidelines on CKD, which included a classification system for CKD severity, independent of the cause, and applicable to both children and adult.[5] In 2003, these guidelines were reviewed and recommended for use in children with CKD.[6] Prior to the introduction of this classification, various thresholds were used. For example, the ItalKid Project, a prospective, population-based Italian study on CKD epidemiology, and the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS), defined CKD as having a glomerular filtration rate (GFR) of below 75 mL/min/1.73 m^2.[7,8] Others based their definition on serum creatinine levels or on other thresholds of GFR.[9]

CKD is now defined as the presence of kidney damage (identified by the presence of abnormalities in blood, urine, imaging studies or kidney biopsy) for ≥ 3 months or a GFR < 60 mL/min/1.73 m^2 for ≥ 3 months (Table 1).[6]

The K/DOQI guidelines emphasize persistent proteinuria as a particularly important marker of kidney damage. The rationale for including individuals with normal GFRs is that substantial kidney damage often occurs before this pivotal component of kidney function declines. The rationale for including individuals with GFR < 60 mL/min/1.73 m^2 without any other evidence of kidney damage is that reduction of kidney function below this level represents loss of at least 50% of normal kidney function, a level at which the prevalence of complications of CKD begins to increase.[6]

Table (1): Criteria for the definition of CKD [6]

A patient has CKD if either of the following criteria are present:

1. kidney damage for ≥ 3 mo, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifest by 1 or more of the following features:
   - Abnormalities in the composition of blood or urine
   - Abnormalities in imaging tests
   - Abnormalities on kidney biopsy
2. GFR <60 mL/min/1.73 m^2 for ≥3 mo, with or without other signs of kidney damage described above

The K/DOQI classification system identifies five stages of CKD based on the level of GFR.[6]

Stage I is defined by a normal GFR (≥ 90 mL/min /1.73 m^2). Stages II - IV are characterized by a GFR of 60-89, 30-59, and 15-29 mL/min /1.73 m^2, respectively. Stage V is characterized by a GFR of <15 mL/min/1.73 m^2 or being on dialysis (end stage renal disease: ESRD) (Table 2). The K/DOQI guidelines stated that in children and adolescents, the GFR should be estimated from prediction equations (like the Schwartz[10]or Counahan-Barrat formulas [11]) that take into account the serum creatinine concentration and the patient's height and gender; and provide much more practical methods for estimating GFR than the cumbersome-and often inaccurate-methods that use 24-hours urine,[6] specimens. The K/DOQI classification system of CKD was widely adopted after its introduction; however, its limitations and possible modifications have been a matter of extensive discussion.[12]

Table (2): NKF-K/DOQI classification of the stages of CKD [6]

Stage	GFR(mL/min/1.73m^2)	Description	Action Plan*
1	≥ 90	Kidney damage with normal or increased GFR	Treat primary and comorbid conditions Slow CKD progression CVD risk reduction
2	60-89	Kidney damage with mild reduction of GFR	Estimate rate of progression of CKD
3	30-59	Moderate reduction of GFR	Evaluate and treat complications
4	15-29	Severe reduction of GFR	Prepare for kidney replacement therapy
5	< 15 (or dialysis)	Kidney failure	Kidney replacement therapy

* The actions that are listed in the more severe stages of CKD also include actions from less severe stages.
CVD indicates cardiovascular disease.

Epidemiology:

Most of the available epidemiological data on CKD in children stems from ESRD registries, and information on the earlier stages of pediatric CKD is still limited. This is

because early stages of CKD in children are often asymptomatic and therefore under-diagnosed and under-reported worldwide. Even less is known in low-income countries where data is mostly obtained from reports of tertiary care referral centers and the validity of this data is variable.[9]

The magnitude of CKD varies from one geographical area to another due to genetic and environmental factors. Various studies report prevalence of CKD ranging from 15-75 cases per million children.[13] Even though the age categories and the definition of CKD differed among countries, the incidence in Europe was fairly consistent, being around 11-12 per million of the age-related population (pmarp) for CKD stages III–V, and 8 pmarp for CKD stages IV-V.[9] The prevalence ranged from about 55-60 to 70-75 pmarp in Spain and Italy, depending on the clinical definition of CKD that was used in each study.[9] A study on the epidemiology of CKD conducted in several Latin American countries showed a wide variation in incidence that ranged from 2.8 to 15.8 new cases pmarp.[14] In a study from Kuwait,[15] the mean incidence was found to be as high as 38 pmarp, whereas the prevalence increased from 188 in 1996 to as high as 329 pmarp in 2003. An incidence of 11 pmarp and a prevalence of 51 pmarp have been reported in Jordanian children.[16] Two reports from Vietnam have suggested an annual incidence of hospitalization for CKD of around 5 pmarp, and most of the patients had already reached ESRD.[17, 18] In a study from Nigeria, the reported incidence of CKD was 11 pmarp and the prevalence was 48 pmarp.[19] In a recent publication based on a true population frequency in Turkey the reported prevalence of childhood CKD stages II-V approached 1%.[20]

There are marked variations in the incidence and prevalence of ESRD in the pediatric population across countries. The median incidence of ESRD in children less than 20 years in 2008 was around 9 pmarp (4 in Russia, 9.5 in Western Europe and Australia, 15 in the United States and 18 in New Zealand).[9] The prevalence of ESRD in 2008 was around 65 pmarp in Australia, Canada, Western Europe and Malaysia, but higher in the United States (85pmarp) and lower in Japan (34 pmarp).[9] Critically, the incidence and prevalence of all stages of CKD in children continues to increase worldwide, and in the United States between 2000 and 2008, the incidence of ESRD rose from 5.9 to 15 pmarp.[9,21]

Etiology:

In children, CKD may be the result of congenital, inherited, metabolic or acquired renal diseases, and the underlying cause correlates closely with the age of the patient at the time when the CKD is first detected. CKD in children <5 years old is most commonly a result of congenital abnormalities such as renal hypoplasia, dysplasia, or obstructive uropathy. Additional causes include congenital nephrotic syndrome, prune-belly syndrome, cortical necrosis, focal segmental glomerulosclerosis, polycystic kidney disease, renal vein thrombosis, and hemolytic-uremic syndrome.[22] After 5 years of age, acquired diseases (various forms of glomerulonephritis including lupus nephritis) and inherited disorders (familial juvenile nephronophthisis, Alport syndrome) predominate. CKD related to metabolic disorders (cystinosis, hyperoxaluria) and certain inherited disorders (polycystic kidney disease) can occur throughout the childhood years.[22] Table (3) presents the etiology of CKD in children.[23]

Table (3): Causes of CKD in children [23]

Congenital abnormalities	Multicystic kidney Renal hypoplasia /dysplasia Vesicoureteral reflux
Obstructive uropathies	Uretheral atresia Posterior uretheral valves Uretero-pelvic junction obstruction
Cystic kidney diseases	Autosomal recessive polycystic kidney disease Autosomal dominant polycystic kidney disease Glomerulocystic kidney diseases
Dysgenetic kidneys	Autosomal recessive renal tubular dysgenesis
Congenital nephrotic syndrome	Autosomal recessive (Finnish type) Diffuse mesangial sclerosis Denys-Drash syndrome Galloway-Mowat syndrome
Neonatal acute renal injury	Asphyxia Renal venous thromboses
Glomerulonephritis	Lupus nephritis IgA nephropathy Henoch-Schönlein purpura nephritis Crescentic glomerulonephritis Alport syndrome
Nephrotic syndrome	Focal segmental glomerulosclerosis Membranoproliferative glomerulonephritis Membranous glomerulopathy
Hemolytic-uremic syndromes (HUS)	Stx HUS Factor H HUS
Tubulointerstitial diseases	Medications Infections Cystinosis, hyperoxaluria Nephronophthisis Pyelonephritis
Renal transplantation	Chronic rejection Immunosuppressive agents Recurrence

Pathogenesis/Progression of CKD:

In addition to progressive injury with ongoing underlying disease, renal injury can progress despite removal of the original insult. Childhood CKD commonly progresses toward ESRD, largely independent of the underlying disorder, once a critical impairment of renal function has occurred.[24] The progression rate of CKD is variable and depends on the underlying disease, severity of the initial injury, the presence of additional risk factors and adequacy of treatment. Data from the NAPRTCS on children with CKD stages II-IV showed a progression rate to ESRD of 17% at 1 year and 39% at 3 years following registration, with a median time to ESRD of 4.5 years.[25] The rate of progression was inversely proportional to base-line GFR. In the ItalKid project, the incidence of renal replacement therapy was 7.3 per year per 100 patients with CKD, and the risk of ESRD was 68% by the age of 20 years.[7]

✓ **Hyperfiltration Injury:**

Hyperfiltration injury may be an important final common pathway of glomerular destruction, independent of the underlying cause of renal injury. As nephrons are lost, the remaining nephrons undergo structural and functional hypertrophy characterized by an increase in glomerular blood flow. The driving force for glomerular filtration is thereby increased in the surviving nephrons. Although this compensatory hyperfiltration temporarily preserves total renal function, it can cause progressive damage to the surviving glomeruli, possibly by a direct effect of the elevated hydrostatic pressure on the integrity of the capillary wall and/or the toxic effect of increased protein traffic across the capillary wall. Over time, as the population of sclerosed nephrons increases, the surviving nephrons suffer an increased excretory burden, resulting in a vicious cycle of increasing glomerular blood flow and hyperfiltration injury.[22]

✓ **Factors that Influence CKD Progression Rate:**

A. Non-Modifiable Risk Factors:

1. Fetal Programming

Low birth weight (even after correction for gestational age) is associated with an increased risk of CKD and ESRD. Although the mechanisms have not been fully elucidated, a congenital defect in nephron number appears to be important. The proposed mechanisms linking nephron number and CKD risk revolve around the increased hypertension risk due to associated changes in natriuresis and glomerulosclerosis caused by intraglomerular hyperfiltration. [26]

2. Ethnicity

For reasons that may pertain to genetic, environmental and/or socioeconomic factors, certain races are more likely to develop ESRD. Risks may be due to a higher incidence of certain disease or a more aggressive clinical course for specific disease entities. African Americans have a higher incidence of hypertensive nephrosclerosis and idiopathic focal segmental glomerulosclerosis. These diseases, together with lupus nephritis and HIV nephropathy, are also more aggressive in African Americans.[27] Hispanic patients also have a worse prognosis than Caucasians.[28]

3. Puberty

It is commonly perceived that renal function deteriorates more rapidly around the time of puberty. Increased body mass at puberty was thought to be associated with systemic and intrarenal hemodynamics that accelerate glomerular and interstitial fibrosis.[29]

4. Underlying renal disease and genetic pathology

It is evident that patients with aggressive, incompletely controlled nephropathies will have a more rapid progression of renal failure than subjects with renal hypoplasia. Also, in disease entities caused by defects in more than one gene, progression pattern may differ according to the gene involved. For example, in children with mutations in the NPHP1 gene, ESRD is attained at a mean age of 13 years as compared with 8 months in those with NPHP2 mutations.[30]

B. Modifiable Risk Factors:

1. Hypertension

Hypertension occurs in 20% to 80% of children with CKD depending on the degree of renal dysfunction and underlying renal disease.[24] It is one of the most critical determinants of progression rates in children with CKD. The pathophysiology is complex but increased activity of the renin-angiotensin system plays a central role and impaired renal arteriolar autoregulation makes the kidney an especially vulnerable target organ. The ensuing glomerular hyperfilteration is implicated in the genesis of glomerulosclerosis and proteinuria which is thought to induce inflammation and fibrosis within the interstitial compartment.[31] It has recently been shown that aggressive treatment of blood pressure to below the 50th percentile has significant renoprotective effect in children.[32]

2. Proteinuria

In virtually every epidemiological study, the degree of proteinuria emerges as a significant independent predictor of CKD progression rate. This correlation is even true for non-glomerular diseases such as reflux nephropathy where urinary protein/creatinine ratios greater than 0.8 were associated with faster deterioration.[31,33] Treatment designed to lower urinary protein excretion results in slowing down GFR decline.[31] There is experimental evidence that proteins in the glomerular ultrafiltrate may gain access to the interstitium through breaks in Bowman's capsule or disruptions in glomerulotubular junctions; where they exert a direct toxic effect on tubular cells and recruit monocytes and macrophages, enhancing the process of glomerular sclerosis and tubulointerstitial fibrosis.[34]

3. Hyperphosphatemia

There is reasonable evidence that hyperphosphatemia is an independent risk factor for more rapid renal function decline. This is attributed to calcium-phosphorus deposition in tubular mitochondria, renal interstitum and blood vessels.[35]

4. Dyslipidemia

Epidemiological data suggest that dyslipidemia - which is common in CKD - is independent risk factor not only for cardiovascular disease but also for faster rates of renal functional decline. The dyslipidemic pattern differs between the major renal disease entities and the degree of dyslipidemia parallels the degree of renal function impairment. Dyslipidemia may damage glomerular capillary and mesangial cells as well as podocytes through oxidant mediated injury. The possible renoprotective efficacy and safety of statin in children with CKD, as yet has not been established.[30, 36]

5. Anemia

There is increasing evidence that anemia is an independent risk factor for progression of CKD.

Anemia results in tissue hypoxia, increased oxygen consumption and enhanced production of reactive oxygen species and these perpetuate preexisting renal tissue damage. Erythropoietin has been found to significantly slow renal disease progression in some but not all studies.[24,31]

6. High protein intake

Animal studies have shown that high protein diet results in renal scarring whereas restriction of dietary protein diminishes or even prevents renal damage. This led to the hypothesis that restriction of protein intake might also slow down the progression of renal dysfunction in patients with CKD stages II-IV.[24]

Pathophysiology:

CKD may be viewed as a continuum of disease, with increasing biochemical and clinical manifestations as renal function deteriorates.[22] The pathophysiologic (biochemical and clinical) consequences of CKD and their mechanisms are outlined in Table 4.

✓ Acidosis and electrolyte abnormalities

Metabolic acidosis can cause negative nitrogen balance, increased protein degradation and decreased albumin synthesis leading to protein-energy malnutrition, loss of lean body mass and muscle weakness. Metabolic acidosis can also alter vitamin D and parathyroid hormone levels, causing bone demineralization, and may suppress native growth hormone secretion.[37]

Failure of sodium and free water excretion in stage V CKD, leads to extracellular volume expansion, manifesting clinically as peripheral edema and pulmonary edema. In earlier stages of CKD, a similar picture can occur if the ingested amounts of sodium and water exceed the available potential for compensatory excretion.[38] However, during infancy, CKD is often caused by polyuric salt-wasting conditions such as obstructive uropathy, renal dysplasia, tubular disease or polycystic kidney disease. This leads to hyponatremia, decreased extracellular volume and impaired growth.[39] Hyperkalemia usually develops when the GFR falls below 20% of normal. However, hyperkalemia may develop in earlier stages of CKD if the dietary intake is increased or angiotensin-converting enzyme inhibitors are used.[40]

Table (4): Pathophysiology of chronic kidney disease*

MANIFESTATION	MECHANISMS
Accumulation of nitrogenous waste products	Decreased GFR
Acidosis	Decreased ammonia synthesis Impaired bicarbonate reabsorption Decreased net acid excretion (reduced nephrons)
Sodium retention	Excessive renin production Oliguria
Sodium wasting	Solute diuresis Tubular damage/dysfunction
Renal concentrating defect (polyuria)	Solute diuresis Tubular damage/dysfunction
Hyperkalemia	Decreased GFR Metabolic acidosis Excessive potassium intake Hyporeninemic hypoaldosteronism
Renal osteodystrophy	Impaired renal production of 1,25 dihydroxycholecalciferol Hypocalcemia Hyperphosphatemia (↓GFR) Secondary hyperparathyroidism
Malnutrition	Inadequate caloric intake^{+} Increased protein degradation Decreased albumin synthesis Proteinuria
Growth retardation	Malnutrition Renal osteodystrophy Metabolic acidosis Anemia Growth hormone resistance
Anemia	Decreased erythropoietin production Iron deficiency (true&functional) Folate deficiency Vitamin B_{12} deficiency Decreased erythrocyte survival
Bleeding tendency	Defective platelet function
Infection	Defective granulocyte function Impaired cellular immune functions Indwelling dialysis catheters
Neurologic symptoms (fatigue, poor concentration, headache, drowsiness, memory loss, seizures, peripheral neuropathy)	Uremic factor(s) (toxins) Hypertension Aluminum toxicity
Gastrointestinal symptoms (anorexia, nausea, vomiting, bleeding)	Gastroesophageal reflux Decreased gastrointestinal motility Ulcers

Hypertension	Volume overload Excessive renin production
Hyperlipidemia/Dyslipidemia	Decreased plasma lipoprotein lipase activity Insulin resistance Acidosis
Pericarditis, cardiomyopathy, heart failure	Uremic factor(s) Hypertension Fluid overload Vascular calcification Anemia
Glucose intolerance	Tissue insulin resistance

*Adapted from references 22&37
+ Due to anorexia, emotional distress, altered taste sensation, nausea and vomiting

✓ Calcium, Phosphorus and Renal Osteodystrophy

Hypocalcemia becomes evident when the GFR is <30 mL/min/1.73 m^2. The threshold, at which serum phosphorus level starts to increase, ranges from 20 to 50 mL/min/1.73 m^2. High calcium-phosphorus product occurs with lower GFR, leading to precipitation in the kidneys and vessels.[23]

The term renal osteodystrophy is used to indicate a spectrum of bone disorders seen in children with CKD. The most common disorder seen is "high-turnover bone disease" caused by secondary hyperparathyroidism. The skeletal pathological finding in this condition is osteitis fibrosa cystica. Adynamic bone disease "low-turnover bone disease" may occur as a result of excess treatment with vitamin D analogs and calcium salts, leading to over suppression of the parathyroid hormone (PTH); and the pathologic finding of osteomalacia. It is characterized by low PTH and alkaline phosphatase and high serum calcium level; and is associated with increased risk of vascular calcification; fractures and more severe growth retardation.[22,23,42]

Clinically, renal osteodystrophy presents with muscle weakness, bone pain, fractures with minor trauma and signs of rickets, deformities and may be slipped capital femoral epiphysis.[22]

✓ Growth retardation

The NAPRTCS reported that more than one third of children with CKD exhibited significant growth failure. Significant short stature was seen at all stages of CKD, with a correlation between renal function and growth impairment.[43]

✓ Anemia

Anemia is usually manifesting in patients with stages III-IV CKD, and is present in all patients with stage V CKD. Anemia is typically normocytic, normochromic and hypoproliferative.[44]

Clinical Presentations:

Antenatal pointers to CKD include oligohydramnios, polyhydramnios, and abnormal antenatal ultrasound findings. The presence of a syndrome should prompt evaluation of the

kidneys and urinary tract. Incidental findings such as single umbilical artery, hypospadius and low-set ears, are rare but important indicators of CKD.[23]

The clinical presentation of CKD is varied and depends on the extent of renal function deterioration and the underlying disease. Patients with mildly diminished renal reserve (stage II) are asymptomatic. Even patients with mild-moderate renal insufficiency may have no symptoms, despite elevated blood urea nitrogen (BUN) and creatinine unless they get dehydration or infection that can precipitate severe azotemia.[22]

Accordingly, early recognition of CKD requires keeping a high index of suspicion especially in the situations listed in Table 5. In infants and young children with CKD, most of the symptoms are vague and non-specific, but failure to thrive is an important sign of CKD. Fatigue, headache, anorexia, nausea, and vomiting occur relatively late.[22,23,37]

However, infants with congenital disorders such as renal dysplasia, and obstructive uropathy can present in the neonatal period with failure to thrive, polyuria, dehydration, urinary tract infection or overt renal insufficiency.[22,23]

Older children and adolescents may present with lassitude, polydipsia, nocturia, forgetfulness, falling grades at school or delayed puberty. Children with CKD from chronic membranoproliferative glomerulonephritis can present with edema, hypertension, hematuria and proteinuria.[22,23]

The physical examination in children with CKD can reveal pallor and sallow appearance. Long standing untreated cases can have short stature, wasting and signs of rickets. [22]

In end-stage renal disease, severe metabolic, neurologic, cardiovascular, intestinal, hematologic and skeletal abnormalities are present.[45]

Table (5): High index of suspicion of CKD [37]

1. Abnormal renal imaging
2. Unexplained anemia
3. Unexplained failure to thrive or short stature
4. Bony deformities
5. Recurrent urinary infections
6. Polyuria
7. Systemic disease with known renal involvement
8. Hypertension
9. Persistent proteinuria and abnormal urinalysis
10. Positive family history of kidney disease
11. Exposure to nephrotoxic drugs

Psychological and Cognitive Effects of CKD:

Children with CKD often experience growth retardation and altered body image and frequently miss school and other normative activities, thereby affecting their psychological development and increasing depression among them.[46] Children with CKD reported poorer overall health-related quality of life (HRQOL) scores and poorer physical, school, emotional and social domain scores compared to healthy children.[47]

Twenty to forty percent of children with CKD scored at least one standard deviation below normative data on measures of intelligence quotient, academic achievement, attention regulation, and executive functioning.[48]

Work-up:

1. Urinalysis

Urinalysis is a basic test for the presence and severity of kidney disease. It detects proteinuria, hematuria, pyuria, casturia, bacteriuria and specific gravity (urine concentrating capacity). Proteinuria is an early and sensitive marker of kidney damage. The most appropriate, and precise method for estimation of proteinuria in children is to calculate the protein or albumin-to-creatinine ratio in a spot urine specimen (preferably a first morning specimen). In some specific types of CKD (diabetic nephropathy, hypertension) screening for microalbuminuria provides an early marker of hyperfiltration.[23,37,49]

2. Estimation of glomerular filtration rate

The GFR is the best measure of overall kidney function. The normal GFR varies with age, gender and body size (Table 6).[6] Inulin clearance is the gold standard to determine GFR, but it is not easy to measure. Endogenous creatinine clearance is the most widely used marker of GFR but it may be imprecise if 24-hour urine collection is incomplete, and is compromised by tubular creatinine secretion that falsely elevates the GFR. Several other markers of GFR are under investigation to accurately determine the GFR in children such as cystatin C and iohexol.[22]

The K/DOQI guidelines stated that all children with CKD should have an estimated GFR calculated from the Schwartz (or Counahan-Barratt) prediction equation, because it is convenient, reasonably precise, and practical.[6,50]

The estimated GFR using Schwartz formula:

$$\text{eGFR (mL/min/1.73m}^2\text{)} = \frac{\text{k x height "cm"}}{\text{serum creatinine"mg/dl"}}$$

Where k is 0.33 for low-birth weight infants <1 year old, 0.45 for term infants <1 year old whose birth weight is appropriate for gestational age, 0.55 for children and adolescent girls, and 0.70 for adolescent boys.[10,50,51]

Table (6): Normal GFR in children and adolescents[6]

Age (sex)	Mean GFR ±SD (mL/min/1.73m^2)
1wk (males and females)	41±15
2-8wk (males and females)	66±25
>8wk (males and females)	96±22
2-12y (males and females)	133±27
13-21y (males)	140±30
13-21y (females)	126±22

SD=standard deviation

3. CBC and Serum Chemistry

Complete blood count (CBC) and serum chemistry are important investigations both in the initial evaluation and subsequent follow-up of children with CKD. The hemoglobin level rather than the hematocrit value should be used as the standard assessment for anemia, as the hematocrit may vary from changes in volume status, body temperature and blood sugar.[4] Blood urea nitrogen and serum creatinine measurements are the most important tests. However, they do not rise outside the normal range until the residual renal function is < 70% of normal.[49]

Estimation of serum sodium, potassium, calcium, phosphorus, bicarbonate, alkaline phosphatase, parathyroid hormone, albumin, cholesterol and fractionated lipid levels are important in the treatment and prevention of various complications of CKD.[22,49]

4. Imaging studies [4,37,49]

All patients with CKD should undergo ultrasonography. It may reveal normal, small or large kidneys, hydronephrosis, or loss of corticomedullary differentiation. Increased cortical echoes is a non-specific but sensitive indicator of glomerular, interstitial or vascular diseases. Ultrasonography is also important for monitoring renal growth and for detecting post-voiding residual urine.

Voiding cystourethrogram can be performed to detect vesicoureteral reflux and posterior uretheral valves. CT scan may be performed for renal masses. The benefits of studies employing iodinated contrast agents (antegrade pyelography or CT scan) should be weighed against the potential risk of acute kidney damage. Radionuclide studies may be used for detection of renal scarring, reflux nephropathy and vesicouretral reflux.

Chest X-ray and echocardiography should be performed for evaluation of cardiac disease (left ventricular hypertrophy and dysfunction) in children with advanced CKD. Skeletal radiography is indicated in advanced CKD with severe secondary hyperparathyroidism, where subperiosteal mineral resorption may be seen especially in the

phalanges of the hands. It is also indicated for determination of bone age before starting and during growth hormone therapy.

5. Renal Biopsy

A renal biopsy is commonly performed in patients with glomerular diseases or vasculitis and in those with otherwise unexplained CKD. If a child has a small shrunken kidney, the kidney biopsy is often unnecessary.

In advanced stages of CKD, irrespective of the underlying etiology, the findings often consist of segmental and globally sclerosed glomeruli, tubular atrophy, and interstitial fibrosis, often with tubulointerstitial mononuclear infiltrates.[37,49]

Management:

Children with CKD should be treated at a pediatric center capable of supplying multidisciplinary services including medical, nursing and social services as well as nutritional and psychological support.[22]

Objectives [37,49]

The treatment of CKD aims at:

- Specific therapy based on etiologic diagnosis.
- Regular monitoring of clinical and laboratory status.
- Evaluation and management of reversible causes of renal dysfunction.
- Retarding progression of CKD.
- Initiation of conservative/supportive therapy for complications of decreased kidney function (acidosis, anemia, hypertension, bone disease, growth retardation, etc.).
- Psychosocial evaluation and support.
- Preparation for renal replacement therapy (RRT).
- Initiation of RRT once indicated.

The K/DOQI has proposed an action plan for each stage of CKD. For a child with stage I 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 stages II and III it is important to regularly estimate the rate of progression of CKD while ensuring a constant evaluation and treatment for co-morbid conditions. At stage IV, preparations for renal replacement therapy are initiated, since by stage V it is imperative to provide this therapy. [6]

Management of reversible causes of renal dysfunction

The various factors or clinical states that may have aggravated the degree of renal dysfunction must be determined. Once these factors are corrected or reviewed, the severity

of kidney failure may improve, and kidney function may return to stable basal level of function. The common reversible causes include volume depletion, drugs (non-steroidal anti-inflammatory drugs: NSAIDs, contrast agents), infection (urinary or systemic), and congestive heart failure.[49]

Retarding progression of renal disease

Several strategies may be effective in slowing progression of CKD, the most important are strict control of blood pressure and measures to reduce proteinuria. The blood pressure should be maintained at lower than the 75th percentile. Angiotensin-converting-enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) even in the absence of hypertension, have potential renoprotective effect by reducing proteinuria, lowering intraglomerular pressure, and exerting antifibrotic effect.[22,37]

Serum phosphorus should be maintained in the normal range for age, and the calcium-phosphorus product < 55 to minimize renal calcium phosphate deposition. Prompt treatment of infections and episodes of dehydration can minimize additional loss of renal parenchyma. Other beneficial interventions include correction of anemia, control of hyperlipidemia and avoidance of nephrotoxic medications (e.g NSAIDs). For hyperlipidemia or dyslipidemia, reduction of dietary saturated fat and cholesterol intake are recommended. Statin therapy may be considered in children older than 10 years if fasting LDL remains above 100 mg/dL. Although dietary protein restriction has been shown to be useful in adults, it is not suggested for children with CKD because of the adverse effect on growth and development.[4,22,37]

Fluid, Electrolyte and Acidosis Management

Fluid restriction is rarely necessary in children with CKD until the development of ESRD. Children with hypertension, edema or heart failure, require sodium restriction and diuretic therapy. Infants and children with renal dysplasia or reflux nephropathy may be polyuric with significant urinary sodium losses. These children require high-volume, low-caloric density feedings with sodium supplementation.[4,22]

Potassium homeostasis is usually preserved until stage V is reached. However, hyperkalemia can develop in patients with moderate renal insufficiency who have excessive dietary potassium intake, severe acidosis, hyporeninemic hypoaldosteronism or receiving ACEIs, ARBs or potassium-sparing diuretics. Hyperkalemia may be treated by restriction of dietary potassium intake, administration of oral alkalinizing agents, and/or treatment with kayexalate.[4,22]

Metabolic acidosis develops when the GFR declines below 50% of normal. Oral sodium bicarbonate should be given to maintain serum bicarbonate value of greater than 22 mEq/L to maximize growth.[4,22]

Nutrition

Infants and children with CKD should be prescribed a calorie intake according to the estimated energy requirements for age, sex and body weight. Protein intake should be between 100% and 140% of the dietary reference intake for children with CKD stage III and between 100% and 120% for children with CKD stages IV&V. Proteins should be of high biological value that are metabolized primarily to usable aminoacids rather than to

nitrogenous wastes. The proteins of highest biologic value are those of eggs and milk, followed by meat, fish and chicken. Infants should receive a low phosphate formula. Caloric intake may be enhanced in infants by supplementing the formula with modular components of glucose polymers, medium-chain triglyceride oil and protein as tolerated. If weight gain and growth velocity remain suboptimal tube feeding or gastrostomy should be considered. Supplementary water-soluble vitamins are frequently needed. Iron and zinc should be added if deficiencies are confirmed.[4,22]

Growth

Children with CKD who remain less than -2SD for height despite optimal medical supplement (adequate nutrition, and effective treatment of metabolic acidosis, anemia, and renal osteodystrophy) might benefit from treatment with pharmacologic doses of recombinant human growth hormone (rHuGH). Treatment may be initialized with 0.05 mg/kg/24hr of rHuGH subcutaneously, with periodic adjustment of the dose to achieve a goal of normal height velocity for age. Treatment with GH should continue until the patient reaches the 50th percentile for midparental height or undergo kidney transplantation.[4,22,37,43]

Renal Osteodystrophy (ROD)

Infants and children with CKD should follow a low phosphorus diet or formula. Phosphate binders are used to enhance fecal phosphate excretion, the most commonly used are calcium carbonate or gluconate, and are given with meals. The recommended total (diet and binders) intake of calcium for children with CKD is twice the daily dietary recommended average for age. New non-calcium-based binders such as sevelamer (120-160 mg/kg/day) are increasingly in use, particularly in patients prone to hypercalcemia. Aluminum-and citrate-based binders should be avoided in children.[4,22,37]

The cornerstone of therapy for ROD is vitamin D administration. Patients with a normal 25-hydroxy-vitamin D but elevated parathyroid hormone should be treated with 0.01-0.05 mcg/kg/24 hr of calcitriol. Newer activated vitamin D analogs such as paricalcitol and doxercalciferol are increasingly used especially in patients predisposed to hypercalcemia. Phosphate binders and vitamin D should be adjusted to maintain the PTH level within the designated goal range and the serum calcium and phosphorus levels within the normal range for age, and the calcium-phosphorus product at <55 to minimize the possibility of tissue deposition of calcium-phosphorus salts.[4,22,37,53]

Anemia

Iron therapy is indicated if there is iron deficiency and during treatment with erythrocyte- stimulating agents (ESAs). Oral iron should be taken 2 hr before or 1 hr after calcium- based phosphate binders and food to maximize absorption. Intravenous iron is indicated if there is no satisfactory response to oral therapy. ESAs are indicated when the iron status is adequate and the hemoglobin level is below 10 g/dL. Recombinant human erythropoietin (rHuEPO) is initiated at a dose of 100-150 IU/kg/week subcutaneously in 1-2 doses. The dose is adjusted to maintain the hemoglobin level between 11 and 12 g/dL, not more than 13g/dL. An alternative option is darbepoetin alfa, a longer acting ESA administrated at a dose of 0.45 mcg/kg/week subcutaneously; but it can be dosed once weekly to once monthly. Blood transfusions are best avoided in order to reduce the risk of

sensitization in potential transplant recipients, iron overload and transmission of infectious agents. Symptomatic severe anemia may need red blood cell transfusions with the use of leukocyte filters.[4,22,37,54]

Hypertension

Target blood pressure in children and adolescents with CKD should be lower than the 90th percentile for normal values adjusted for age, gender, and height or 120/80 mmHg, whichever is lower. More recent studies suggest that maintaining blood pressure below the 50th percentile may be effective in delaying progression of kidney disease.[37]

Hypertensive children with suspected volume overload should follow a salt-restricted diet (2-3g/24hr) and can benefit from diuretic therapy. Thiazide diuretics are the initial diuretics of choice in CKD stages I-III (hydrochlorothiazide 2mg/kg/24hr divided bid). In stage IV, thiazides are less effective and loop diuretics (furosemide 1-2 mg/kg/dose bid or tid) become the diuretic class of choice.[4,22,37]ACEIs and ARBs are the antihypertensive medications of choice in all children with proteinuric renal disease because of their potential ability to slow the progression to ESRD. Extreme care must be used with these agents, however, to monitor renal function and electrolyte balance, particularly in children with advanced CKD. Calcium-channel blockers (amlodipine), beta-blockers (propranolol, atenolol), and centrally acting agents (clonidine) may be useful as adjunctive agents in children with CKD whose blood pressure cannot be controlled by the aforementioned measures.[4,22,37]

Immunizations

Children with CKD should receive all standard immunizations according to the schedule used for healthy children. However, live vaccines are contraindicated while on immune-suppressive therapy or within 6 weeks of their discontinuation. All children with CKD should receive a yearly influenza vaccine. Children with CKD may have a reduced response to and/or reduced duration of antibody after immunization and therefore monitoring for antibody titers is indicated for some vaccines such as hepatitis B vaccine. [22,37,55]

Drug dosage adjustment

Because many drugs are excreted by the kidneys, impaired renal function would lead to accumulation of these drugs as well as their metabolites, with increasing risk of toxicity. Modification of the drug dosage is usually necessary only when the GFR is less than 30-40 mL/min/1.73m^2. Strategies in dosage adjustment include lengthening the interval between doses, decreasing the individual doses or both. In patients on dialysis, the dosage of some drugs need to be adjusted.[22,55,56]

Psychosocial support

It is crucial to have ongoing involvement of child psychologists / psychiatrists, medical social workers, and counselors in dealing with the multifaceted problems of CKD in children. Appropriate measures need to be taken to address issues concerning family dynamics, coping skills, decision making, adherence to therapy as well as financial issues. Patient education focuses on health monitoring, home care, adherence to medications, schooling, growth and maturational issues. Early assessment of neurodevelopmental and cognitive abilities and emotional status of children is prudent so that individualized

educational plans and counseling may take place and educational, emotional, and functional potential may be optimized. [4,37,57]

Preparation for renal replacement therapy (RRT)

It is recommended that plans for RRT (dialysis or renal transplantation) be initiated when a child reaches stage IV CKD, as progression to ESRD will inevitably develop. Formal discussions regarding planning of RRT should be multi-disciplinary, including not just the family and nephrologist but also the surgeons, specially trained nurses, social workers, dieticians, and psychologists. The plans should include preparation of the vascular access, completion of necessary surgical procedures (such as nephrectomy, cystoplasty, gastrostomy) as well as completion of necessary immunizations (particularly live vaccines) before RRT. Unnecessary blood transfusions should be avoided to minimize antigen exposure prior to transplantation. [4]

Renal Replacement Therapy

In ESRD, homeostasis and survival can no longer be sustained with native kidney function and maximal medical management. At this point renal replacement therapy (dialysis or renal transplantation) becomes necessary. The ultimate goal for children with ESRD is successful kidney transplantation. [22]

The majority of children with ESRD require a period of dialysis before transplantation can be performed. However, pre-emptive transplantation before initiation of dialysis is increasingly being used. The optimal time to initiate dialysis is based on a combination of laboratory and clinical criteria including GFR < 15 mL/min/1.73m^2, refractory fluid overload, electrolyte imbalance, acidosis, growth failure, or uremic symptoms, including fatigue, nausea and impaired school performance. In general, most nephrologists attempt to initiate dialysis early enough to prevent the development of severe fluid and electrolyte abnormalities, malnutrition, and uremic symptoms. [22,37]

The selection of dialysis modality must be individualized to fit the needs of each child. In the USA, 2/3 of children with ESRD are treated with peritoneal dialysis (PD), whereas 1/3 are treated with hemodialysis (HD). Age is a defining factor in dialysis modality selection: 88% of infants and children from birth to 5 years of age are treated with PD, and 54% of children >12 years of age are treated with HD. [22]

Peritoneal dialysis can be performed at home manually as continuous ambulatory peritoneal dialysis (CAPD) or with an automated device (cycler: continous cycling PD). CAPD is typically performed with four exchanges (of dialysate) during the day and a long night-time dwell with very meticulous attention for maintaining asepsis. CAPD provides near steady-state biochemical control with minimal need for dietary and fluid restrictions. [58]

Hemodialysis is usually performed in a hospital setting. Children and adolescents typically have 3-to 4-hr sessions per week, during which fluid and solute wastes are removed. In developed countries home nocturnal hemodialysis is becoming a feasible option. [22,59]

Renal transplantation offers (in comparison with the dialysis option) better renal functions, a decrease in morbidity and mortality, improved quality of life, and improved growth, nutrition and school performance. The donor source could be a living related (parents, grandparents, siblings above 18 years of age or first degree relatives) or an unrelated individual or a deceased donor. Current 1-and 5- year patient survival rates for pediatric living donor kidney transplants are 98% and 96%, respectively, and for pediatric deceased donor transplant are 97% and 93%, respectively. [60, 61]