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Management Therapy of Chronic Kidney Disease in Children

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Abstract
Chronic Kidney Disease (CKD) refers to a condition with an irreversible kidney damage that can progress to end-stage renal disease. CKD in childhood presents clinical features that are specific and give an impact to the pediatric age. . The prevalence of CKD is about 1.5 to 3.0 per 1,000,000 among children younger than the age of 16 years per year. The main etiologic factors of CKD in children are caused by congenital abnormalities of the kidney and urinary tract, steroid-resistant nephrotic syndrome, chronic glomerulonephritis and renal ciliopathies. Chronic Kidney Disease is a disease that affects multiple systems, including calcium-phosphorus metabolism, growth, hematologic and cardiovascular systems. The general management of children with CKD includes treating reversible kidney dysfunction, preventing the progression of CKD and treating the complications associated with CKD.

Keywords*: Chronic Renal Failure, CKD, pediatrics, management*

A. INTRODUCTION

Chronic Kidney Disease (CKD) refers to a condition with an irreversible kidney damage that can progress to end-stage renal disease (ESDR) (Harambat, Kim, & Tizard, 2012). CKD is also called chronic renal disease or chronic kidney failure. It affects people of all ages and races (KDIGO, 2012). The prevalence of CKD is common increase globally and an incidence rate of 8%, it is about 1.5 to 3.0 per 1,000,000 among children younger than the age of 16 years or 82 cases per million per year (Halle, et al., 2017; Whyte & Fine, 2008). CKD is defined as abnormalities of kidney structure or function, present for >3 months or longer, with or without decreased Glomerulus Filtration Rate (GFR); or GFR less than 60 mL/min/1.73 m^2 for 3 months or longer, with or without kidney damage. Kidney function is decreased, and it gets worse over time. CKD in childhood presents clinical features that are specific and give an impact to the pediatric age. CKD not only influencing the health of the patient in childhood and their adult life, but also giving a psychosocial impact, both on the patient and family (Becherucci, Roperto, Materassi, & Romagnani, 2016). This review will focus on the clinical features and management CKD in children.

B. CHRONIC KIDNEY DISEASE IN CHILDREN

a. Classification of CKD

The KDOQI Group classified CKD in children into five stages (Table 1). Glomerular filtration rate (GFR) values for CKD staging are for children older than 2 years of age because the GFR values for younger children are low due to ongoing renal maturation (Whyte & Fine, 2008). In adults, the rate of albumin excretion is also included in the staging of CKD based on data that correlates the level of albuminuria to outcome. However, similar data are lacking in children. As a result, albuminuria is not used to classify pediatric CKD. Children under two years of age do not fit within the above classification system because they normally have a low GFR even when corrected for body surface area and their renal is still ongoing maturation (Wong, Warady, & Srivastava, 2016).

Table 1. Chronic Kidney Disease Classification (National Kidney Foundation, 2002)

Stage	Description
1	Kidney damage with a normal or increased GFR (>90 mL/min per 1.73 m^2)
2	Mild reduction in the GFR (60 to 89 mL/min per 1.73 m^2)
3	Moderate reduction in the GFR (30 to 59 mL/min per 1.73 m^2)
4	Severe reduction in the GFR (15 to 29 mL/min per 1.73 m^2)
5	Kidney failure (GFR<15 mL/min per 1.73 m^2 or dialysis)

b. Etilogy

The causes of CKD are very different in children than in adults. Adult CKD is caused by diabetic nephropathy, hypertension and autosomal dominant polycystic kidney disease (Kaspar, Bholah, & Bunchman, 2016). The main etiologic factors of CKD in children are caused by congenital abnormalities of the kidney and urinary tract (CAKUT), steroid-resistant nephrotic syndrome (SRNS), chronic glomerulonephritis and renal ciliopathies. Urologic abnormalities and glomerulopathies are account for more than 50% of the reported causes ESRD in children (Becherucci, Roperto, Materassi, & Romagnani, 2016; Whyte & Fine, 2008). In addition,

the risk of developing ESRD in adolescence are increased in infants with infants of low birth weight and small for gestational age (Vikse, Irgens, Leivestad, Hallan, & Iversen, 2008; Carmody & Charlton, 2013).

c. Clinical features and Treatments of CKD

A moderate to severe loss of glomerular filtration rate (GFR), may result in a number of complications due to renal impairment (Figure 1)

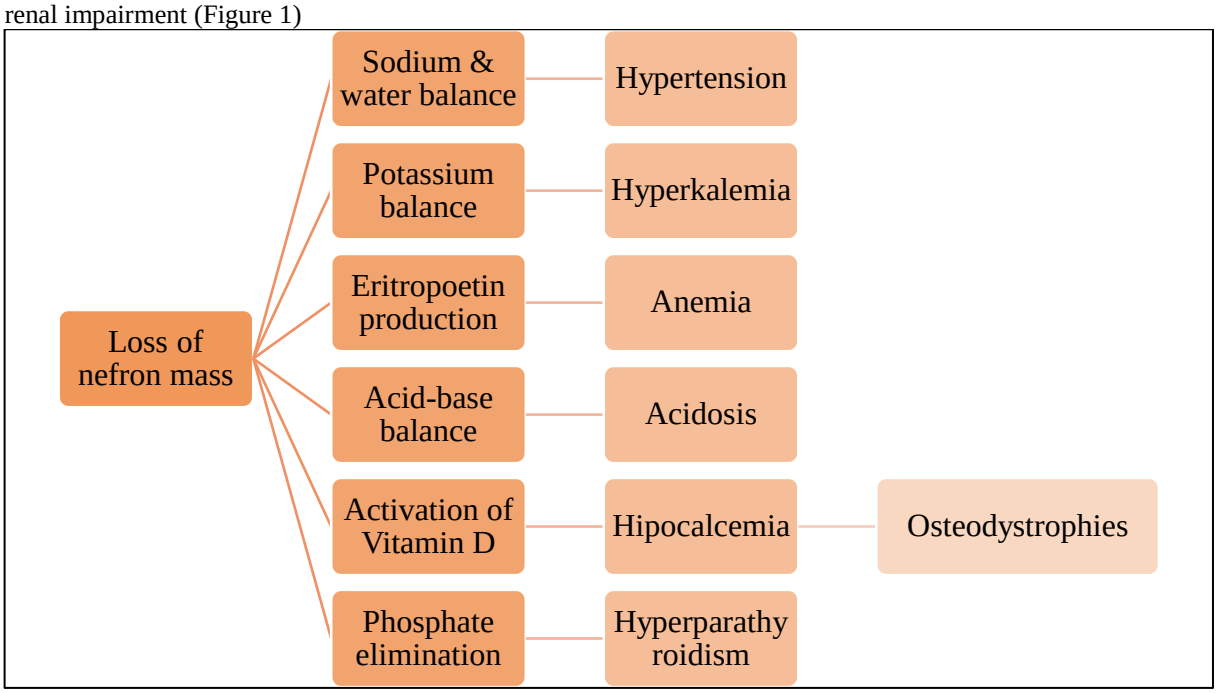

Figure 1. Complications in Chronic Kidney Disease (Perlman, Heung, & Ix, 2014)

i. Electrolyte Disorders

CKD cause an abnormally decreased bicarbonate reabsorption, reduced synthesis of renal ammonia, decreased acidified tubular fluid, and decreased titratable acid excretion. Abnormally bicarbonate reabsorption leads to systemic acidosis that causes protein degradation and efflux of calcium from. Therapy in metabolic acidosis should target maintaining a serum bicarbonate are concentration of 20 to 22 mEq/L. Sodium bicarbonate supplements or phosphate binders used to bicarbonate replacement (Whyte & Fine, 2008).

In the healthy kidney, maintenance of potassium homeostasis is the secretion of potassium into the distal convoluted tubule and the proximal collecting duct. As renal disease progresses, the distal tubules of the remaining nephrons continue to secrete potassium. Increased aldosterone also enhances potassium secretion by stimulating sodium-potassium exchange in the kidneys and the colon. The nephrons ability to an acute increase in potassium load resulting in the development of hyperkalemia (Kovesdy, 2014; Whyte & Fine, 2008). Managements of hyperkalemia are low potassium diet (restriction 2 g/day), minimization or elimination of any medication that may impair renal potassium excretion (i.e spironolactone, NSIADs, ACE inhibitors, ARBs, beta-blockers), Administration of a loop diuretic to increase urinary potassium loss (0.5 to 2 mg/kg per day) (Watnick & Dirkx, 2016; Whyte & Fine, 2008).

ii. Renal Osteodystrophy

Disturbances in homeostasis calcium-phosphate and bone metabolism are clinical problems in almost all patients with CKD. The broader clinical syndrome that develops as systemic complication of abnormalities in mineral and bone metabolism and extra-skeletal calcification are called CKD-mineral and bone disorder (CKD-MBD). Renal osteodystrophy (including CKD-MBD) occurs due the complex disturbances of calcium and phosphorus metabolism, parathyroid hormone (PTH), active vitamin D, and possibly fibroblast growth factor-23 (FGF-23) homeostasis (Figure 2). A typical pattern seen as early as CKD stage 3 is hyperphosphatemia, hypocalcemia, and hypovitaminosis D, resulting in secondary hyperparathyroidism. (Watnick & Dirkx, 2016; Kemper & Husen, 2014).

PTH is released by the parathyroid glands which contain calcium-sensing receptors that trigger PTH secretion when extracellular calcium decreases. PTH has little effect due to low vitamin D and high serum phosphate concentrations (phosphorus cannot be secreted by the diseased kidneys) as well as downregulation of PTH

receptors (Leiker, et al., 2013; Whyte & Fine, 2008). Vitamin D increases calcium and phosphorus absorption in duodenum and jejunum. Vitamin D converts to 25-hydroxyvitamin D (calcidiol) by 25-hydroxylase in liver, which is the primary form vitamin D in blood. Then in kidney, 1α-hydroxylase converts calcidiol to the active form calcitriol. PTH increases 1α-hydroxylase in the kidney, producing more catcitriol which increased reabsorption of calcium and phosphorus (Leiker, et al., 2013).

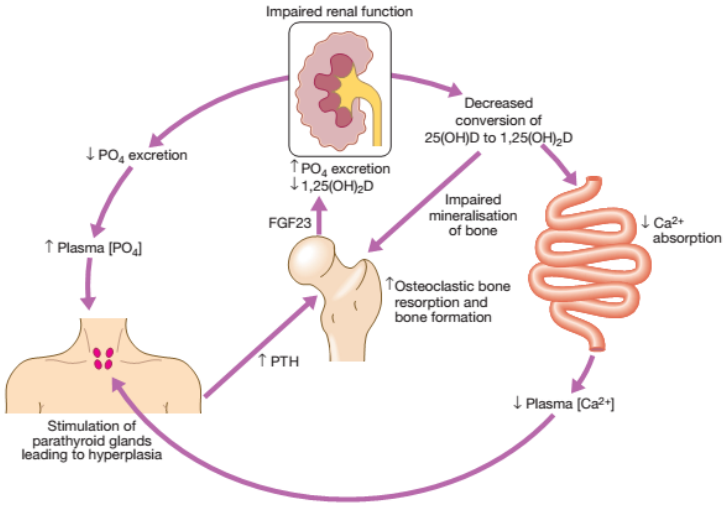

Figure 2. Pathogenesis of renal osteodystrophy. Low $1,25(OH)_2D$ levels cause calcium malabsorption and this, combined with high phosphate levels, causes hypocalcaemia, which increases PTH production by the parathyroid glands. The raised level of PTH increases osteoclastic bone resorption and bone formation. Although production of FGF23 from osteocytes also increases, promoting phosphate excretion, this is insufficient to prevent hyperphosphataemia in advanced CKD (Goddard & Turner, 2015)

Hyperparathyroidism can be treated by administration of active vitamin D metabolites, which may raise the serum levels of calcium and phosphorus. In children with uncontrolled hyperparathyroidism (undergoing dialysis), activators of the calcium receptors on parathyroid cells have been found to be effective agents to control CKD-MBD when other treatment ineffective (Massengill & Ferris, 2014).

Abnormal bone mineralization can occur the fractures and osteitis fibrosa. Secondary hyperparathyroidism with renal osteodystrophy possibly leading to alterations in the normal growth plate cartilage architecture (Whyte & Fine, 2008). Optimization of bone health and growth must be a focus of CKD management in children. The goal therapy is to normalize mineral metabolism, reducing bone deformities and minimizing the progression of skeletal calcification Dietary restriction can control phosphate level but very rarely adequate and phosphate binders, which can be calcium-based compound or non-calcium-containing compounds, become necessary (Rees & Shroff, 2015; Becherucci, Roperto, Materassi, & Romagnani, 2016).

iii. Anemia

Anemia in CKD is primarily due to decreased erythropoietin production, which often becomes clinically significant during stage 3 CKD. Anemia is result of many factors, but decreased production of erythropoietin by the unhealthy kidney and iron dysregulation (including iron deficiency and iron-restricted erythropoiesis) are the primary defects. Many patients are iron deficient as well due to impaired GI iron absorption (Watnick & Dirkx, 2016; Becherucci, Roperto, Materassi, & Romagnani, 2016).

The anemia of CKD is principally normocytic and normochromic. Although the exact level of GFR at which anemia develops is not well defined, one study of children with CKD reported that anemia began to develop at a measured GFR threshold of 43 mL/min per 1.73 m^2. A major goal of anemia management is to avoid the need for blood transfusions that may increase antibody sensitization and adverse impact access to kidney transplantation. If left untreated, the anemia of CKD is associated with fatigue, weakness, decreased attentiveness, increased somnolence, and poor exercise tolerance. Children with better hemoglobin levels have improved quality of life, cognitive and cardiovascular function (Wong, Warady, & Srivastava, 2016).

The treatment of anemia in children with CKD includes iron supplementation and an erythropoiesis stimulating agent (ESA). Iron therapy (3 to 4 mg/kg per day) should be initiated if iron deficiency is detected. Treatment with recombinant human erythropoietin (rHuEPO) is safe and effective for children with CKD and in maintenance dialysis condition. Dosage rHuEPO in young children require higher doses than adults, ranging

from 275 U/kg to 350 U/kg per week for infants, to 200-250 U/kg per week for older children (Becherucci, Roperto, Materassi, & Romagnani, 2016). Adjunctive therapies can include treating other nutritional deficiencies and controlling bone mineral metabolism disorders (Atkinson & Furth, 2011).

iv. Hypertension

Unlike many of the complications of CKD, hypertension (HTN) can be present in the earliest stages of CKD, due to volume expansion and/or activation of the renin-angiotensin system, and its prevalence increases as GFR progressively declines (Wong, Warady, & Srivastava, 2016).

The prevalence of HTN in children is 3% to 9%, however in children in CKD, the prevalence rises to 50% (Gallibois, Jawa, & Noone, 2017). Hypertension is diagnosed in children who have CKD by finding an elevated blood pressure reading on three or more separate office visits at least 1 week apart and it is based on the child's age, sex, and height percentile. Grades of hypertension are as follows, based on tables or graphs of normal values (Table 3) (Whyte & Fine, 2008).

Three main risk factors for CKD progression are HTN, nephron mass and proteinuria. These factors are linked and have compounding effects to one another. Loss of nephron mass leading hyperfiltration and increased GFR (Noone & Licht, 2014). Proteinuria is common in pediatric CKD, that caused either by damage to the glomerular capillary wall or by decrease in tubular reabsorption of protein leading destruction of the renal tubular cells. Management HTN in CKD is essential to improve prognosis of pediatric patients and antihypertensive intervention can preventing end-organ damage (Gallibois, Jawa, & Noone, 2017). The recommend target systolic and diastolic blood pressures by The National Kidney Foundation's KDOQI guidelines is less than 90th percentile for age, gender and height (K/DOQI, 2004).

Table 3. Grades of hypertension in children ((Whyte & Fine, 2008)

Grade	Description
Prehypertension	Average systolic or diastolic pressures are at the 90th percentile or greater but at or less than the 95th percentile for age, sex, and height
Stage I hypertension	Average systolic or diastolic pressure is at or greater than the 95th percentile for age, sex, and height
Stage II hypertension	Average systolic or diastolic pressure is more than 5 mm Hg higher than the 95th percentile
Hypertensive urgency and emergency	Average systolic or diastolic pressure is more than 5 mm Hg higher than the 95th percentile and clinical symptoms of headache, vomiting, seizures, or encephalopathy are present

Many antihypertensive drugs are available for children based on extrapolation from adult dosage recommendations or clinical experience (Table 4). The first line therapy for HTN in CKD is renin angiotensin aldosterone system (RAAS)-acting agents. The main drug therapy used in children consists of ACE inhibitors. The predominant antihypertensive effects of ACEis is inhibition of angiotensin II production and there is a renal protective effect that adds their value as first line therapy. Angiotensin receptor blockers (ARB) directly block the action of angiotensin II on their cell membrane receptors. Combination ARBs and ACEis has increased for patients with chronic renal failure as renoprotective regimen to reduce proteinuria and delay progression of renal disease. ACEis and ARBs are drugs of choice for patients who have chronic glomerular disease and diabetes mellitus (Gallibois, Jawa, & Noone, 2017; Feld & Corey, 2007).

Table 4. Antihypertensive Drugs for Management of Hypertension in Children 1 to 17 years of Age (Feld & Corey, 2007)

Class	Drug	Dose (interval)	Adverse effect/Special consideration of Each Class
Angiotensin Converting Enzyme Inhibitor (ACEi)	Captopril	I: 0.3 to 0.5 mg/kg per dose (tid); M: 6 mg/kg per day	Periodically measure serum creatinine and potassium concentrations Cough and angioedema are less common with new ACEis
	Lisinopril	I: 0.07 mg/kg per d up to 5 mg/d; M: 0.6 mg/kg per d up to 40 mg/d	
	Enalapril	I: 0.08 mg/kg per day up to 5 mg/d (once daily-bid); M: 0.6 mg/kg per day up to 40 mg/d	

			Consider for renoprotective effect for renal disease with proteinuria and diabetes mellitus
Angiotensin Receptor Blocker (ARB)	Irbesartan	6 to 12 y: 75 to 150 mg/d (once daily) >13 y: 150 to 300 mg/d	Periodically measure serum creatinine and potassium concentrations FDA approval is limited to children >6 y of age and creatinine clearances >30 mL/min per 1.73m2
	Losartan	I: 0.7 mg/kg per day up to 50 mg/d (once daily); M: 1.4 mg/kg per day up to 100 mg/d	
Calcium Channel Blocker	Amlodipine	Children 6 to 17 y: 2.5 to 5 mg once daily	extended-release nifedipine tablets must be swallowed whole May cause tachycardia and edema
	Extended-release nifedipine	I: 0.25 to 0.5 mg/kg per day (once daily-bid); M: 3 mg/kg per day up to 120 mg/d	
Alpha and Beta Blocker	Labetalol	I: 1 to 3 mg/kg per d (bid); M: 10 to 12 mg/kg per day up to 1,200 mg/d	Asthma and overt heart failure are contraindications Should not be used in those who have insulin-dependent diabetes
Beta Blocker	Atenolol	I: 0.5 to 1 mg/kg per day (once daily-bid) M: 2 mg/kg per day up to 100 mg/d	Noncardioselective agents (propranolol) are contraindicated in those who have asthma and heart failure
	Propranolol	I: 1 to 2 mg/kg per day (bid-tid); M: 4 mg/kg per day up to 640 mg/d	
Class	**Drug**	**Dose (interval)**	**Adverse effect/Special consideration of Each Class**
Diuretics	Hydrochlorothiazide	I: 1 mg/kg per day; M: 3 mg/kg per day up to 50 mg/day	May cause severe hyperkalemia, especially in conjunction with ACEi or ARB Furosemide is useful adjunctive therapy for patients who have renal disease
	Furosemide	I: 0.5 to 2 mg/kg per day (once daily-bid)	
	Spironolactone	I: 1 mg/kg per day (once daily-bid) M: 3.3 mg/kg per day up to 100 mg/d	

I = Initial; M = Maximum

Calcium Channel Blockers (CCBs) are vasodilators that inhibiting calcium transport into vascular smooth muscle, thereby limiting contractility and vasoconstriction. They are used as first-line therapy for patients that contraindicated with ACEis and in children with inadequate effect of ACEis/ARBs alone. Beta Blockers have several mechanism including decreased cardiac output, decreased peripheral vascular resistance, inhibition of renin secretion, inhibition of sympathetic activity and decreased circulating plasma volume. Another drug that can used for hypertension in children is diuretics. Diuretics inhibit absorption of solute and decrease reabsorption of water and enhance urine flow (Halbach & Flynn, 2015; Feld & Corey, 2007).

v. Growth Retardation

Impairment of growth in children can begin when the GFR falls to 50% of normal and becomes an increasing problem once the GFR falls below 25%. Growth hormone therapy can used with indications: (1) that continuing growth retardation despite the correction of insufficient nutrition, fluid and electrolyte disorders, metabolic acidosis, anemia and renal osteodystrophy, (2) Glomerular filtration rate less than 75 mL/min per 1.73 m^2, (3)

being below the 3rd percentile for age and gender (−1.88 standard deviation score) or a standard deviation score below −2 for age and gender. one year of 28 IU/m²/week rhGH (Recombinant human growth hormone) in children with CKD, regardless of their pubertal and treatment status (pre-dialysis, dialysis, post-transplant), results in an average height increase of 3.88 cm/year (Hodson, Wilis, & Craig, 2012).

C. CONCLUSION

Chronic Kidney Disease is a disease that affects multiple systems, including calcium-phosphorus metabolism, growth, hematologic and cardiovascular systems. The general management of children with CKD includes treating reversible kidney dysfunction, preventing the progression of CKD and treating the complications associated with CKD.

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