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End Stage Renal Disease: Review Article

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Abstract:

End-stage renal disease (ESRD) represents the final stage of chronic kidney disease (CKD) and is defined by a severe and irreversible decline in kidney function, with a glomerular filtration rate (GFR) of less than 15 mL/min. CKD is a progressive condition characterized by structural or functional kidney abnormalities persisting for more than three months, commonly assessed by reduced GFR and increased albuminuria. The burden of ESRD is increasing worldwide and is associated with significant morbidity, mortality, and healthcare costs. In pediatric populations, CKD is predominantly caused by congenital and hereditary disorders, unlike adults where diabetes and hypertension are the leading causes. The progression to ESRD involves complex pathophysiological mechanisms including nephron loss, compensatory hyperfiltration, and subsequent glomerular damage, ultimately leading to metabolic disturbances such as hyperkalemia, metabolic acidosis, anemia, and bone disease. Early detection and appropriate management are essential to delay disease progression and improve patient outcomes.

Keywords: End-stage renal disease; Chronic kidney disease; Pediatric nephrology; Glomerular filtration rate; Hemodialysis; Renal replacement therapy.

Introduction:

More than 500,000 people in the United States live with end-stage renal disease (ESRD). The development of chronic kidney disease (CKD) and its progression to this terminal disease remains a significant cause of reduced quality of life and premature mortality **(1).**

The Kidney Disease Improving Global Outcomes (KDIGO) foundation guidelines define CKD using kidney damage markers, specifically markers that determine proteinuria and glomerular filtration rate. By definition, the presence of both factors (glomerular filtration rate (GFR) less than 60 mL/min and albumin greater than 30 mg per gram of creatinine) along with abnormalities of kidney structure or function for greater than three months signifies chronic kidney disease. End-stage renal disease is defined as a GFR of less than 15 mL/min **(2).**

According to the updated KDIGO clinical practice guideline, with subsequent reaffirmation in later KDIGO updates, chronic kidney disease is classified into five stages based on the level of estimated glomerular filtration rate (eGFR), reflecting the severity of renal dysfunction and risk of complications **(3, 4).**

- Stage 1: Kidney damage with normal GFR (greater than 90 ml/min)
- Stage 2: Mild reduction in GFR (60-89 mL/min)
- Stage 3a: Moderate reduction in GFR (45 to 59 mL/min)
- Stage 3b: Moderate reduction in GFR (30 to 44 mL/min)
- Stage 4: Severe reduction in GFR (15 to 29 mL/min)

- Stage 5: Renal failure (GFR less than 15 mL/min)

Etiology

In pediatric patients, the etiology of chronic kidney disease differs from adults and is predominantly related to congenital and hereditary abnormalities, glomerular diseases, and tubulointerstitial disorders, while acquired causes such as hypertension play a lesser role compared to adult populations. In children, chronic kidney disease is mainly caused by congenital anomalies of the kidney and urinary tract, hereditary nephropathies, and glomerular diseases, whereas acquired causes such as hypertension are less common than in adults **(5).**

Table (1): Main Causes of Chronic Kidney Disease in Children **(5).**

Category	**Examples**
Congenital anomalies of the kidney and urinary tract (CAKUT)	Renal hypoplasia, renal dysplasia, vesicoureteral reflux, obstructive uropathy
Glomerular diseases	IgA nephropathy, minimal change disease, focal segmental glomerulosclerosis (FSGS)
Hereditary kidney diseases	Alport syndrome, polycystic kidney disease
Tubulointerstitial diseases	Interstitial nephritis, metabolic or genetic tubular disorders
Urinary tract obstruction or dysfunction	Posterior urethral valves, neurogenic bladder
Unresolved acute kidney injury	Progression from AKI to CKD
Drug-induced kidney injury	NSAIDs, calcineurin inhibitors, some antivirals

Epidemiology

According to the United States Renal Data System, in 2015, there were 124,411 new ESRD diagnoses, reflecting an increasing burden of kidney failure. The prevalence of the disease has been rising at a stable number of about 20,000 cases per year. Kidney disease is the ninth leading cause of death in the United States **(6).**

Sex

The cumulative incidence of end-stage renal disease is higher in males than females **(7).**

Pathophysiology

Each nephron in a normal kidney contributes to the total glomerular filtration rate (GFR). The decline of kidney function is gradual and may initially present asymptomatically. The natural history of renal failure depends on the etiology of the disease but ultimately involves early homeostatic mechanisms involving hyperfiltration of the nephrons. The kidney maintains GFR, despite the progressive destruction of nephrons because the remaining normal nephrons develop hyperfiltration and compensatory hypertrophy. As a result, the patient with mild renal impairment can show normal creatinine values, and the disease can go undetected for some time **(8).**

This nephron adaptability allows for continued normal clearance of plasma solutes. This adaptive mechanism will run its course and eventually cause damage to the glomeruli of the remaining nephrons. At this point, antihypertensives such as ACEs or ARBs may be beneficial in slowing the progress of the disease and preserving renal function. Plasma levels of substances such as urea and creatinine start to show measurable increases only after total GFR has decreased by 50%. For example, a rise in plasma creatinine from 0.6 mg/dL to 1.2 mg/dL in a patient, although within the normal range, actually represents a loss of 50% of functioning nephron mass **(7).**

Although hyperfiltration and hypertrophy of residual nephrons are beneficial for maintaining GFR, it is found to be a major cause of progressive renal dysfunction. The increased glomerular capillary pressure may damage the capillaries, leading to focal and segmental glomerulosclerosis (FSGS) and eventually to global glomerulosclerosis **(9).**

Hyperkalemia

Hyperkalemia is defined as an abnormally elevated serum potassium level resulting from impaired renal potassium excretion **(10).**

Potassium excretion at near-normal levels is generally maintained in CKD as long as aldosterone secretion and distal flow are maintained. Hyperkalemia develops when GFR falls to less than 20-25 mL/min/1.73 m^2; at this point, the kidneys have decreased ability to excrete potassium **(11).**

Metabolic Acidosis

Metabolic acidosis in stage 5 CKD is high anion gap metabolic acidosis but with the anion gap generally not higher than 20 mEq/L. In CKD, the kidneys cannot produce enough ammonia in the proximal tubules to excrete endogenous acid into the urine in the form of ammonium. In stage 5 CKD, the accumulation of phosphates, sulfates, and other organic anions is the cause of the increase in the anion gap **(12).**

Metabolic acidosis has deleterious effects on protein balance, leading to the following **(7)**:

- Negative nitrogen balance
- Increased protein degradation
- The increased essential amino acid oxidation
- Reduced albumin synthesis
- Lack of adaptation to a low-protein diet

Metabolic acidosis also plays a role in the development of renal osteodystrophy because bones are buffers for excess acid, with a resultant loss of minerals. Acidosis also interferes with vitamin D metabolism **(7)**.

Salt and Water Handling Abnormalities

Salt and water handling by the kidney are affected in CKD. Volume overload results from the failure of sodium and free-water excretion and occur when the GFR falls to less than 10-15 mL/min/1.73 m^2. This leads to peripheral edema, pulmonary edema, and hypertension. Tubulointerstitial renal diseases often cause fluid loss rather than overload. Thus, despite severe reductions in GFR, tubulointerstitial renal diseases may manifest as polyuria and volume depletion, with the inability to concentrate the urine (**13**).

Anemia

Normochromic normocytic anemia develops from the decreased renal synthesis of erythropoietin, the hormone responsible for bone marrow stimulation for red blood cell (RBC) production. Other causes of anemia in CKD include the following **(14):**

- Chronic blood loss: Uremia-induced platelet dysfunction enhances the bleeding tendency

- Secondary hyperparathyroidism
- Inflammation
- Nutritional deficiency

Bone Disease

Renal bone disease is a common complication of CKD. Different types of bone disease occur with CKD, as follows:

- High-turnover bone disease from high parathyroid hormone (PTH) levels
- Low-turnover bone disease (adynamic bone disease) **(15).**
- Defective mineralization (osteomalacia)
- Mixed disease
- Beta-2-microglobulin–associated bone disease

Secondary hyperparathyroidism develops in CKD because of the following factors:

- Hyperphosphatemia
- Hypocalcemia
- Decreased renal synthesis of 1,25-dihydroxycholecalciferol (1,25-dihydroxyvitamin D, or calcitriol)
- Intrinsic alteration in the parathyroid glands gives rise to increased PTH secretion and increased parathyroid growth **(16).**
- Skeletal resistance to PTH

Hyperphosphatemia develops from the inability of the kidneys to excrete excess phosphate. Hyperphosphatemia suppresses the renal hydroxylation of inactive 25-hydroxyvitamin D to calcitriol. Increased phosphate concentration also affects PTH concentration by directly affecting the parathyroid glands (posttranscriptional effect). Hypocalcemia results from decreased intestinal calcium absorption because of low plasma calcitriol levels. Hypocalcemia, hyperphosphatemia, and low serum calcitriol levels stimulate PTH synthesis and secretion. With persistent stimulus in advanced CKD, parathyroid glands become hypertrophic and then hyperplastic **(7)**.

Clinical and Physical examination

End-stage renal disease can present with a constellation of signs and symptoms. Some include volume overload refractory to diuretics, hypertension poorly responsive to medication, anemia, mineral and bone disorders, and metabolic derangements including hyperkalemia, hyponatremia, metabolic acidosis, hypo/hypercalcemia, and hyperphosphatemia. Metabolic acidosis in stage 5 CKD presents protein-energy malnutrition, muscle weakness, and loss of lean body mass. Salt and water retention can cause peripheral edema, pulmonary edema, and hypertension. Anemia manifests as fatigue, impaired cognitive function, and reduced quality of life. Anemia can also lead to heart failure**(17).**

ESRD symptoms generally appear in stages 4 and 5 when the GFR is less than 30 ml/min. Some patients with nephrotic syndrome and cystic renal disease may present earlier. Depression is ubiquitous in patients with ESRD and should be screened for on presentation **(18).**

Prognosis

End-stage renal disease is a progressive disorder, and timely renal replacement therapy is necessary to prevent death. The disorder is associated with numerous hospitalizations, increased healthcare costs, and

metabolic changes. The mortality rates for patients with end-stage renal disease are significantly higher than those without the disease. Even with timely dialysis, the death rates vary from 20% to 50% over 24 months. The most common cause of death isadverse cardiac events.Cardiovascular disease represents the leading cause of mortality in patients with end-stage renal disease, while electrolyte disturbances, including hyperkalemia, contribute significantly to fatal cardiac arrhythmias. Mortality rates are higher for men than women; similarly, Blacks are more prone to death due to ESRD than Whites. The highest mortality rate is within the first six months of starting dialysis. The 5-year survival rate for a patient undergoing long-term dialysis in the United Statesis approximately 35% and about 25% in patients with diabetes **(19).**The 5-year survival rate of patients undergoing long-term dialysis in Egypt is relatively low compared to high-income countries, largely due to late presentation, limited resources, and high burden of comorbidities, particularly diabetes and cardiovascular disease **(20).**

In children, puberty is delayed in both genders, and low vitamin D levels are common, an independent risk factor for death **(21).**

Management of end-stage renal disease in children focuses on optimizing growth and development, correcting metabolic and electrolyte abnormalities, ensuring adequate nutrition, and early consideration of kidney transplantation as the preferred renal replacement therapy **(22).**

Hemodialysis

It is well known that amongst renal replacement therapies kidney transplantation is the one that confers the best quality of life and survival. Standard hemodialysis (HD) however remains the most widely used treatment for patients with end-stage renal disease (ESRD), largely due to the rather limited availability of organs. Despite its significant limitations, namely the rather poor quality of life it offers to the patients, poor clearance of middle and large molecular weight substances, high incidence of infections and cardiovascular diseases as well as unacceptably high mortality among dialysis patients, and high cost, standard HD remains a unique treatment modality, offering a life sustaining treatment option for those with end-stage kidney failure, who are either waiting for or unable to receive a kidney transplant. Both the population of patients with ESRD and those on HD follows a constantly increasing trend internationally **(23).**

In Egypt, pediatric end-stage renal disease represents a significant health burden, with congenital anomalies of the kidney and urinary tract and hereditary nephropathies being the leading causes. Although nationwide recent pediatric registries are limited, available data indicate a gradual increase in the prevalence of children requiring renal replacement therapy, largely reflecting improved survival and expanded access to dialysis services **(5, 24).**

In Egypt, the prevalence of dialysis patients has increased from 225 pmp in 1996 to 483 pmp in 2008 (according to last Egyptian renal registry) and the main causes of ESKD in Egypt, other than diabetic nephropathy, included hypertensive kidney disease, chronic glomerulonephritis, unknown etiology, chronic pyelonephritis, schistosomal obstructive uropathy, and schistosomal nephropathy **(20).**

The dynamics of this particular form of renal replacement therapy vary across countries with longer dialysis sessions and slower blood flow rates in Japan. PD is highly prevalent in Hong Kong and the Jalisco region of Mexico, while Home HD is widely adopted in New Zealand and Australia **(25).**

The timing for initiation of dialysis is decided after considering the complications of early initiation (unnecessary exposure to IV lines and invasive procedure with risks of infection) against late initiation causing avoidable volume, metabolic, and electrolyte complications of AKI. It is not advisable to assign an arbitrary urea nitrogen or creatinine level for dialysis initiation due to individual variability in uremia symptom severity and renal function. Despite optimal CKD management, patients progress to needing RRT, especially when their eGFR drops below 20 ml/ min/1.73 m2 or they rapidly deteriorate to ESRD within 12 months. The eGFR at dialysis initiation has steadily increased in recent times. In 1996, in the United States, 13% of incident ESRD patients started RRT at an eGFR of 10 ml/min/1.73 m2 or higher. This increased to 43% in 2010 and dropped to 39% in 2015. Waiting for uremic symptoms to set in before commencing RRT had added risks of the patient being malnourished with an increased risk of mortality. Asking patients to compare their current eating habits and

physical activity levels with those 6 to 12 months back helps avoid the lack of awareness. The concept of healthy start, with dialysis commencing before the onset of severe uremia symptoms, is associated with prolonged survival. An early start will prepone the need for a change of modality or further procedures without any improvement in the quality of life while adding to healthcare costs. The Renal Physicians Association's (RPA) criteria for identifying dialysis patients with a poor prognosis beyond 75 years of age includes **(26):**

1. Provider's estimation of the likelihood of patient mortality in the next six months
2. Greatly impaired functional status
3. High comorbidity score
4. Severe chronic malnutrition (low serum albumin)

Mortality rates among dialysis patients are markedly higher among younger age groups, primarily attributed to cardiovascular (40%) and infectious causes (10%). High cardiovascular mortality in dialysis patients could be related to shared risk factors such as chronic inflammation, significant changes in extracellular volume, dystrophic vascular calcification, and altered cardiovascular dynamics during dialysis. The study of heart and renal protection (SHARP) having both dialysis and non-dialysis requiring CKD patients showed a 17% reduction in cardiovascular death and major cardiovascular events with simvastatin-ezetimibe treatment. Conventional cardioprotective strategies such as beta-blockers, aspirin, renin-angiotensin-aldosterone system inhibitors are recommended in dialysis patients based on their cardiovascular risk profile. Hypertension has a graded association with ESRD risk as it is both a cause and a consequence of CKD. The first three months after dialysis initiation, especially among older patients, has the highest mortality rates. This could be due to risks associated with the commencement of dialysis (central venous catheter placement) and more severe comorbidities causing deterioration of renal function **(27).**

Indications

Hemodialysis initiation is needed for acute illness associated with **(28):**

- Acute kidney injury
- Uremic encephalopathy
- Pericarditis
- Life-threatening hyperkalemia
- Refractory acidosis
- Hypervolemia causing end-organ complications (e.g., pulmonary edema)
- Failure to thrive and malnutrition
- Peripheral neuropathy
- Intractable gastrointestinal symptoms
- Asymptomatic patients with a GFR of 5-9 mL/min/1.73 m^2
- Any toxic ingestion

Contraindications

Absolute contraindication to hemodialysis is the inability to secure vascular access, and relative contraindications include **(29):**

- Difficult vascular access
- Needle phobia

- Cardiac failure
- Coagulopathy

Modern techniques are employed in patients with extensive vascular disease to improve the establishment and salvaging of vascular access. Relative contraindications like needle aversion can be overcome by careful use of local anesthetics and nursing encouragement. Severe coagulopathy complicates the maintenance of anticoagulation in the extracorporeal circuit **(30).**

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