Review Article

Challenges and Outcomes of Chronic Dialysis in Children: A Narrative Review

Abstract

Chronic dialysis is a life-saving treatment for children with end-stage renal disease (ESRD). However, it comes with difficult challenges, cardiovascular ones being the most significant and fatal. Chronic kidney disease-mineral bone disorder (CKD-MBD) is also a common complication of chronic dialysis, as it has significant effects on growth and cardiovascular health. Infections are alsoasignificant problem for those on chronic dialysis. The cost of dialysis and the lifestyle of Children with CKD are also not optimal, as they have a significantly lower Health-related quality of life (HRQoL) than childrenwith other chronic illnesses. Children on chronic dialysis face several difficult challenges, which differ between peritoneal dialysis (PD) and hemodialysis (HD). Most of these challenges are manageable or preventable. This review article will discuss some of the challenges that children and their families encounter during chronic dialysis strategies to manage these challenges and the outcomes of long-term kidney dialysis.

Keywords: peritoneal dialysis (PD), hemodialysis (HD), chronic kidney disease (CKD), Chronic dialysis, Dialysis complications.

Introduction

The term dialysis comes from the Greek words dia, which means "through," and lysis, which means “splitting”. It is a form of renal replacement therapy (RRT) that enhances the kidneys' role in filtering the blood by using artificial devices that remove excess water, solutes, and toxins when the kidneys cannot do so sufficiently(1,2).There are two methods of dialysis,hemodialysis (HD) and peritoneal dialysis (PD). HD removes uremic toxins and fluids by passing the blood through a vascular access line through an artificial kidney for an average of four hours three times a week. PD removes uremic toxins and fluids from the peritoneum by infusing and draining a special fluid into the abdominal cavity through a PD catheter several times a day. PD is done at home, and HD is done in a hospital or dialysis center, but it can also be done at home(3,4). Chronic dialysisis a life-saving treatment for children with end-stage kidney disease. However, it comes with significant challenges that can affect the child's physical, emotional, and social well-being, with evidence suggesting that mortality rates are significantly higher in younger dialysis patients(1,4).

This review article aims to explore the challenges and outcomes of chronic dialysis in children, including the impact on the cardiovascular system, possible infections, psychosocial adjustment, and the impact of chronic dialysis on the child's lifestyle and family. The article will also discuss the current strategies and interventions in managing complications of chronic dialysis in children.

Cardiovascular system complications

“Chronic kidney disease (CKD) is positively correlated with cardiovascular diseases (CVD); children with CKD have a higher risk of developing CVD than most other pediatric populations, and CVD is considered the most important

comorbidity that limits survival rates in pediatric dialysis patients"(5,6)."In dialysis patients particularly, CVD is accelerated by dialysis, and it causes an increased rate of morbidity and mortality, which is due to an aggregation of risk factors including classic CVD risk factors, CKD-related risk factors, and additional risk factors attributable to dialysis"(5).Figure 1 shows the leading causes of death in the pediatric population in comparison to children on RTT (7).Sudden cardiac death is responsible for 25% of deaths in patients undergoing dialysis(8).

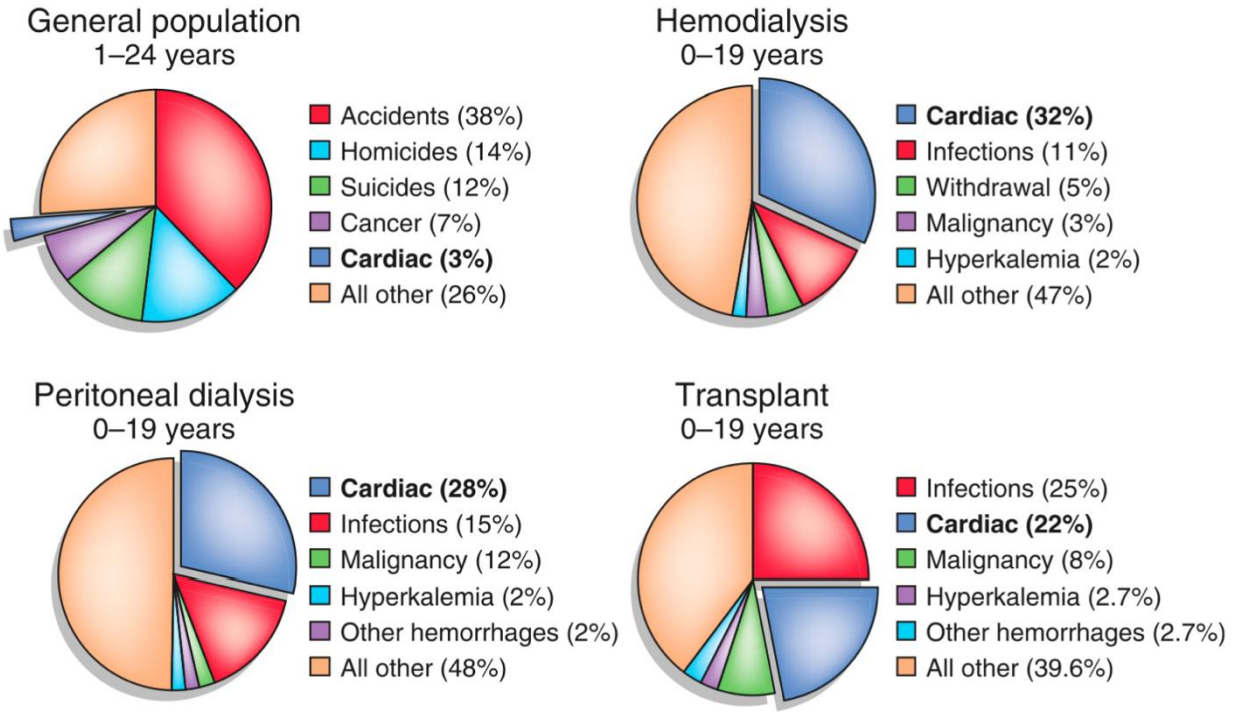

Figure 1Leading causes of death in the general pediatric population and children on RPT. Data for dialysisand transplant patients are from the USRDS (2011) (7).

Chronic fluid overload

"Chronic fluid overload is common in dialysis patients, especially if urine output is low, which leads to left ventricle (LV) hypertrophy because fluid clearance depends on ultrafiltration during dialysis"(7,9). Also, removing large amounts of fluid during HD caused by intradialytic weight loss and sodium and fluid retention further damages the myocardium(10). "Fluid overload also

increases pre-existing hypertension in CKD and is correlated with congestive heart failure (CHF). Management of fluid overload is still one of the most difficult challenges for caregivers of pediatric dialysis patients due to the inaccuracy of dry weight estimation, which is essential for the prevention of fluid overload"(5,11).

Intradialytic hypotension (IDH)

Intradialytic hypotension is themost common complication in HD, its frequency has shown a strong correlation with intradialytic weight gain, cardiac morbidity, and mortality. This is attributable to the hemodynamic stress that is caused by HD, which may cause myocardial ischemia(5,12).

Oxidative stress

Dialysis promotes the accumulation of oxidative products and the discarding of antioxidants; this is more prominent in HD than in PD treatment. Oxidative stress damages organs, proteins, and tissues. It is a major cause of chronic inflammation and anemia; therefore, it contributes to the progression of CVD(5,13,14).

Hypertension

Hypertension is present in 50–75% of children on dialysis. It is considered the most important independent predictor of LV hypertrophy in CKD children; therefore, it is undeniably associated with poor CVD outcomes(7,15,16).Contrary to adults, where hypertension is a primary cause of chronic kidney disease, in pediatric cases, hypertension is mainly a consequence. However, it remains a significant factor that, similar to adults, is likely to contribute to a faster deterioration of kidney function or the advancement of chronic kidney disease to end-stage(17–19).

Anemia

"It is known that the development of LV hypertrophy is a result of volume and pressure overload, and anemia does exactly that by causing a chronic increase

in cardiac output and continual volume overload. It also causes decreased tissue oxygen delivery. A combination of these risk factors may lead to heart diseases, whether ischemic or congestive, and sudden cardiac death"(5,20–22).

Hypoalbuminemia

"Although hypoalbuminemia in dialysis can be caused by inflammation and fluid overload, decreased albumin levels are considered a separate risk factor for cardiac mortality that is not fully dependent on the inflammation and the fluid overload"(5,23).

"Current evidence shows that the management of cardiovascular risk factors is not sufficient, especially anemia and hypertension. Because even short periods of dialysis cause substantial effects on the cardiovascular system, aggressive management and careful monitoring are encouraged"(5).

Chronic kidney disease-mineral and bone disorder

"One complication of chronic kidney disease that is specifically significant because of its effects on growth and cardiovascular health is chronic kidney disease-mineral and bone disorder (CKD-MBD). Kidneys have an important role in controlling calcium and phosphate levels in the body; in early CKD, this control is maintained by compensatory mechanisms"(24,25). "However, children on PD or HD have insufficient phosphate clearance. Plasma calcium, on the other hand, is regulated by different factors some of them are oral intake and dialysis clearance; its levels can be high or low. Increased phosphate levels stimulate parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23) production, which in turn can cause vascular calcification and the demineralization of bone"(26,27). "Regarding the calcium side of things, decreased production of vitamin D by the failing kidneys leads to hypocalcemia, which if not corrected can lead to increased PTH and FGF23, eventually leading to bone demineralization"(28). "Calcium

levels in the blood will increase at this point, which can lead to vascular calcifications"(26)."Management of CKD-MBD remains challenging; children on dialysis can have calcium deficiency, which increases the risk of bone fracture, or excess calcium, which may lead to vascular calcifications. There are few evidence-based studies for guiding clinical practice for children, and Calcium needs differ between children and adults; that's why studies done on adults are not appropriate. Current guidelines recommend keeping calcium and phosphate levels in the age-appropriate range; however, PTH guidelines vary considerably. Intensified dialysis sessions improve phosphate clearance considerably. Phosphate binders as well as native and active vitamin D analogues have been shown to help in the prevention and treatment of CKD-MBD"(29,30).

Infections

Infections caused by dialysis are a major concern for patients undergoing this treatment. Dialysis patients are at increased risk of infection due to the frequently repeated access of their bloodstream via a catheter or fistula. These infections can range from mild skin infections to severe bloodstream infections, which can be fatal. According to the Centers for Disease Control and Prevention (CDC), the most common infections associated with dialysis include bloodstream infections, urinary tract infections, and infections at the site of the access point. To prevent these infections, healthcare providers must be strict in following infection control practices, such as hand hygiene and proper sterilization of equipment. The CDC also recommends that patients receiving dialysis receive the influenza vaccine every year and the pneumococcal vaccine every five years. With proper precautions and preventative measures, the risk of infection can be massively reduced(31–33).

Encapsulating Peritoneal Sclerosis

An uncommon clinical disease called encapsulating peritoneal sclerosis (EPS) is defined by an inflammatory, acquired fibrocollagenous membrane surrounding the small intestine, which causes symptoms similar to intestinal blockage. "A syndrome continuously, intermittently, or repeatedly presenting with symptoms of intestinal obstruction caused by adhesions of a diffusely thickened peritoneum" is how the International Society for Peritoneal Dialysis defines it (34).

EPS can be classified as primary (idiopathic) or secondary, depending on whether the inflammatory process's source can be found. The majority of primary EPS research supports the equatorial predisposition of the condition, although the etiology is still unknown and men are affected 2:1 more frequently than women(35,36). It is possible to identify a systemic or local component that causes peritoneal inflammation in secondary EPS. Medications, infections, mechanical or chemical irritation peritoneal dialysis, cirrhosis, and organ transplantation are among the suspected triggers(37).

Patients with a predisposing condition are thought to experience EPS when a peritoneal inflammatory process (inciting factor) takes place. This is known as the "two-hit" hypothesis in the literature on peritoneal dialysis (PD) (38), where the non-inflammatory peritoneal sclerosis that develops from repeated dialysis sessions is the "first hit" or predisposing state. The cumulative incidence of EPS on PD shows a sharp increase over time, providing evidence in favor of this(39,40) . A cascade of proinflammatory [transforming growth factor β1 (TGFβ1), interleukin-6 (IL-6), CCN2] and proangiogenic [vascular endothelial growth factor (VEGF)] cytokines is initiated by a proinflammatory “second hit” (41–43). TGFβ1 induces peritoneal mesothelial cells to transdifferentiate into mesenchymal cells, which leads to the depletion of mesothelial cells(21,22), increased production of extracellular matrix components [Collagen type 1, alpha 1 (COL1A1)], and

fibrogenesis, which in turn creates a fibro collagenous cocoon(46).The annual incidence of EPS in peritoneal dialysis ranges from 0.14% to 2.5%, more recent studies have shown a decreasing prevalence of EPS, which is probably because of improved dialysis procedures(26,37,47,48). The length of PD is the most important risk factor for the development of EPS with a low cumulative incidence at three years and an increase after five years(16,17,25) . In PD patients, the death rate approaches 50% a year following diagnosis(37,48,49) . The diagnosis is clinical, and a laparotomy or CT scan can confirm it. As of right now, the most extensively researched and widely utilized imaging method for EPS diagnosis is the CT scan. Depending on the disease status and any contraindications, treatment should focus on treating the underlying disease, optimizing diet, and using corticosteroids or tamoxifen alone or in combination. Surgical enterolysis should be taken into consideration for patients who have not responded to conservative medicinal therapy(37).Peritoneal dialysis is an effective treatment for patients with ESRD. However, it does cause certain complications for some patients. One of these complications is peritoneal dialysis-related peritonitis. It is considered the biggest challenge facing the success of peritoneal dialysis. Despite a marked reduction in incidence and mortality rates related to peritoneal dialysis-related peritonitis since its introduction onto the scene in the late 1950s, it is still a major issue that needs addressing(50).The peritoneal dialysis catheter is the source of infection in most cases of PD-related peritonitis. It is a portal of entry for many pathogens. The peritoneum is a place of weak immunity in the body, and it serves as a perfect environment for pathogens, most commonly, the staphylococcal species. Due to this susceptible environment, they can freely proliferate and cause an inflammatory reaction, which is often asymptomatic and is identified by cloudy peritoneal effluent. However, it can present with typical peritonitis features like abdominal pain, distention, and fever(51).

Dialysis and Covid-19

While SARS-CoV-2 infections can affect people of any age, children with CKD receiving regular in-center HD or home PD are more likely to contract infectious disorders like COVID-19 (52). They are susceptible to respiratory virus infections because of their undeveloped immune system, peculiarities of their respiratory tract, and frequent exposure to hospital environments (53). A retrospective study of children on manual physical therapy (PD) ages 0 to 18 was conducted. In comparison to the previous year, we observed a greater incidence of peritonitis in children during the COVID-19 pandemic. During this time, fewer home visits, retraining sessions, and outpatient visits were provided. Our center's previously published study revealed that the majority of children with PD live far from the hospital (54). Due to their immunosuppressed condition and ongoing systemic inflammation, patients with CKDare five times more likely than the general population to experience a severe COVID-19 infection (55,56). The rates of admission to intensive care units, mechanical ventilation, and death are higher among patients with COVID-19 infection who haveCKDand require renal replacement therapy (55,57,58). The COVID-19 pandemic has caused significant disruptions to patients with CKD in terms of quick hospital repurposing, staff and resource shortages, telehealth adoption, infection outbreaks in dialysis units, and the suspension of medical treatments, including kidney transplants(57–61). Concerns have also been raised about the COVID-19 vaccine's long-term access issues and the degree of its efficacy in treating CKD(62).

Psychosocial effect of chronic dialysis

Economic state

Undoubtedly CKD is directly related to the economic state of the patient, the patient needs to make dialysis or kidney transplant, which is Financially expensive, nearly 750,000 persons in the United States have renal failure, accounting for 1% of the Medicare population but accounting for roughly 7% of the Medicare budget. In 2016, Medicare spent $35 billion on individuals with renal failure. In the United States, hemodialysis care costs the Medicare system an average of $90,000 per patient each year, for a total of $28 billion. The total cost of transplant patient care is $3.4 billion(63–65).

PD is less costly than HD in comparison to patients under PD management, patients receiving HDgenerally experienced higher costs. We see a noticeable rise in the cost of treatment in the advanced stage of CKD and this rise affects the economic state of the family of the patient with end-stage renal disease displaying the highest expenditures ($20,110-$100,593), the transition from CKD stage 3 to CKD stages 4-5 was linked with a 1.3-4.2-fold increase in costs from the standpoint of the health system. A reduction of 8-11% in meanEuroQol 5 Dimension 5 Level (EQ-5D) index scores was seen as CKD stages 1-3 advanced into stages 4-5, with stages 4-5 showing the lowest values (0.74-0.79). The number and scope of recent investigations on LE related to various CKD stages in various nations have been constrained. The cheapest treatment option (costing between $14,067 and $80,876), with the highest EQ-5D scores (0.82-0.83), and the longest LE for both sexes across all age categories was a kidney transplant(66).

The economic state is very affected and that makes families have severe financial hardships. A cross-sectional study was carried out on 250 caregivers of children with CKD attending tertiary care hospital/health insurance clinics in Assiut, Egypt using PedsQL™ family impact module (FIM) for assessing family

impact and economic burden between January and May 2018. The results are Only 12.8% of the study's caregivers of children with CKD reported no financial hardship, whereas 60% of them said their children's CKD had caused them severe financial hardship. Selling real estate was the primary coping mechanism employed by careers (21.1%), followed by taking out a loan (11.5%), which can probably affect the quality of treatment(67).

The bad economic state has a bad effect on the patient with CKD and it makes the situation worse. A total of 2914 participants from 14 countries were included in the main analysis. They were randomized into the Safety & Health Achievement Recognition Program (SHARP) and had income data available at both screening and study ends. An additional 1706 participants were included in a sensitivity analysis. The study cohort was followed up for a median of 5.0 years (interquartile range 4.2–5.6). Out of the 2914 participants, 933 (32%) were in the lowest income category for their country at screening, which is known as relative poverty. This group had specific characteristics, such as being older, female, of black ethnicity, less educated, and more likely to have vascular disease and/or diabetes. They were also more likely to be on dialysis at screening compared to those in higher-income groups. The baseline characteristics of participants who were not in poverty at baseline screening but fell into relative poverty (436 [22%] participants) or any lower income category (892 [45%] participants)(68).

Lifestyle

A growing number of studies have evaluated the effects of RRT on the lives of children with ESRD. Numerous difficulties must be overcome by these kids, including numerous hospitalizations, grueling medical procedures, absences from school, and activity limitations. They are therefore susceptible to a wide range of short- and long-term behavioral, emotional, and negative effects, including withdrawing behavior. Pediatric ESRD patients have significantly poorer

HRQoLscores than healthy children of the same age, according to various studies conducted in both Europe and the USA, especially when it comes to physical functioning in those receiving dialysis. Furthermore, children with ESRD had significantly lower HRQoL scores than kids with other chronic illnesses (including diabetes, cardiac conditions, asthma, and severe obesity) on the PedsQL 4.0 domains of physical health, psychological health, social functioning, and school functioning, according to a study from the USA involving 2500 pediatric patients from ten different physician-diagnosed disease clusters(69–71).

The cognitive and social state

In comparison to others of similar age, young adults with childhood-onset CKD stage 5, especially those who have spent more time on dialysis, are more likely to suffer cognitive and learning impairment. Although children with CKD 5 had minor IQ and fine motor coordination abnormalities, Bawden et al.'s neuropsychological tests of sibling pairs revealed no differences in measures of academic success, memory, behavior, or self-esteem. Using health-related quality-of-life indices, more recent research has revealed that children with CKD score lower than healthy controls, but unexpectedly, children on dialysis score higher than one might anticipate, compared to transplant patients. In support of this, Groothoff et al. have demonstrated that, even after accounting for the unavoidable physical issues, the overall subjective health perception of these young adults is surprisingly good. Survivors of prolonged dialysis during childhood have double the chances of being unemployed than the age-matched population. The provision of psychological and educational assistance to children receiving dialysis to address their emotional, educational, and social needs is essential for improving well-being and survival outcomes and must be a core component of patient care(72).

Family role in dialysis

Before starting PD, patients need to be trained on how to do dialysis at home. Understanding how to do dialysis can be difficult for adults, but it can be even more difficult for parents with children. A study was conducted to investigate PD education programs for parents of children with ESRD and to explore issues related to educating parents of children with ESRD. The incidence of peritonitis varied within each hospital and ranged from 0 to 3 episodes per patient-year (median 1.17 episodes per patient-year). There was a significant association between home visits and the incidence of peritonitis ($P<0.01$)(73).

Mortality in patients on dialysis

Overall, there has been a gradual improvement in dialysis mortality since the introduction of dialysis technology in the 1960s. Registry data show that the current adjusted 5-year survival rate is 52% for PD and 42% for HD. PD survival is improving at a higher rate than reported in HD.The most common cause of death among patients receiving PD is cardiovascular diseases, which accounts for 52.7% of all deaths with a known cause, followed by dialysis withdrawal (17.8%), sepsis (9.6%), and other causes (13.3%), including cancer, and respiratory, or gastrointestinal diseases(50).

PD has been performed without major complications in children requiring RRT. However, continuous ambulatory peritoneal dialysis (CAPD) can result in several infectious and non-infectious complications. Infectious complications of PD are frequently reported, but data on non-infectious complications of PD in children are underreported(74).The survival outcomes of patients undergoing HD and PD were found to be comparable. However, certain factors such as high age group and shorter infection-free time were associated with an increased risk of mortality(75).

According to the evidence, patients receiving continuous renal replacement therapy (CRRT) may have a similar risk of mortality compared to those undergoing HD or PD. Nevertheless, PD may be linked to a lower risk of mortality when compared to HD(76).

In the case of patients below the age of 5 who initiated dialysis, the crude mortality rate over 5 years was 57.0 deaths per 1000 patient-years (py) for those who opted for HD, whereas it was 47.3 deaths per 1000 py for those who chose PD. On the other hand, for patients above the age of 5 who initiated dialysis, the mortality rate was 20.6 deaths per 1000 py for HD and 11.1 deaths per 1000 py for PD(77).

The recent advancements and prospects

Currently, more than two million people in the world suffer from ESRD. The best treatment for current patients with ESRD is a kidney transplant (78). Dialysis is initiated when a donor organ is not available. However, two of the most recent technological advancements and innovations in this field are the implantable bioartificial kidney, and kidney regeneration technology. Both techniques are in preclinical stages and aim to fully replace normal kidney functionality. They are considered a fully functioning alternative to long-term dialysis or a donor organ. They improve on previous iterations of renal replacement technology by accomplishing all aspects of normal kidney functionality, while also being fully implantable and autologous to allow patients maximum mobility (79). Another promising prospective cohort study was conducted on 31 hemodialysis children to assess the eff ectiveness of Omega-3 supplements on quality of life among children on dialysis. The study found that the quality of life and adequacy of dialysis improved after n-3FA(Omega-3) supplementation. Some laboratory parameters such as lipid profiles, inflammatory markers, and renal functions have shown

improvements, which encourages its testing for more patients to evaluate its long-term effects and support its routine use. Generally, n-3 FA has shown promising results in changing disease processes involving the inflammatory and immune pathways(80–83).

In summary, while the overall survival outcomes between HD and PD are comparable, factors such as age and infection-free time have been acknowledged as predictors of mortality. Additionally, PD appears to be associated with a lower mortality risk compared to HD, particularly in younger patients. However, further high-quality research is needed to provide a more comprehensive evaluation of mortality outcomes across different dialysis modalities in patients with CKD.

Conclusion

Children on dialysis treatment face many challenges which can be caused or accelerated by the treatment itself. These challenges affect not only the children themselves but also their families. Most of these challenges are manageable or preventable if taken care of correctly. Outcomes of chronic dialysis have improved greatly since the technology has been introduced, with peritoneal dialysis having lesser mortality rates than hemodialysis.

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