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REVIEW

Incremental dialysis: review of the literature with pediatric perspective

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Abstract
Drivers towards initiation of kidney replacement therapy in advanced chronic kidney disease include metabolic and fluid derangements, growth, and nutritional status with focus on health optimization. Once initiated, prescription of dialysis is often uniform despite variability in patient characteristics and etiology of kidney failure. Preservation of residual kidney function has been associated with improved outcomes in patients with advanced chronic kidney disease on dialysis. Incremental dialysis is the approach of reducing the dialysis dose by reduction in treatment time, days, or efficiency of clearance. Incremental dialysis has been described in adults at initiation of kidney replacement therapy, to better preserve residual kidney function and meet the individual needs of the patient. Consideration of incremental dialysis in pediatrics may be reasonable in a subset of children with continued emphasis on promotion of growth and development.

Keywords Children · Dialysis · Kidney replacement therapy · Residual kidney function

Introduction

Dialysis provides a lifesaving therapy for patients with advanced chronic kidney disease who struggle with refractory uremia, acidosis, edema, and metabolic derangements that if untreated are fatal. In pediatric patients, these derangements also stunt growth and development. Dialysis is not without risk and can be associated with increased morbidity from access complications, infections, and the therapy itself. Hence, nephrologists often struggle to identify the ideal time to initiate dialysis, balancing the benefits versus the potential impediments associated with treatment initiation. The IDEAL study, a randomized controlled trial of early (eGFR 10–14 ml/min/1.73 m^2) versus late (5–7 ml/min/1.73 m^2) initiation of dialysis among adults in Australia and New Zealand [1], demonstrated no significant difference between the two groups regarding all-cause mortality, rates of hospitalization, cardiovascular events, or differences in health-related quality of life. Pediatric registry data from 2019 demonstrated that the median eGFR at dialysis initiation is ~ 8 ml/min/1.73 m^2 in both Europe and the USA [2, 3]. Observational data are mixed with timing of initiation of dialysis and outcomes, with some showing increased mortality with early initiation of dialysis [2, 4] and others demonstrating no difference [3].

Once initiated, the prescription of dialysis is often uniform, despite many children initiating dialysis with significant residual kidney function (Kru) and urine production. This prescriptive approach may result in increased morbidity associated with faster loss of Kru [5, 6]. Preservation of Kru among adult dialysis patients is associated with better survival, volume control, reduced dietary restrictions, and reduced inflammation [7, 8]. Data suggests that each increment of clearance provided (or maintained) by Kru is associated with improved outcomes compared to clearance achieved by dialysis [9, 10]. Preserved significant urine output at 1 year is associated with improved survival [11]. Lee et al., comparing the prognostic value of residual urine volume and Kru for survival among 1946 incident dialysis patients in Korea, demonstrated that both residual urine volume (defined as > 100 ml/day) and Kru as measured by average of 24-h urine creatinine and urea clearance were independently associated with reduced mortality risk [12].

Among adult patients with significant Kru, the concept of incremental dialysis is sometimes considered at dialysis

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initiation [13], with the goal to slow the rate of decline of residual kidney function and/or production of urine while adopting the dialysis therapy to best suit the goals of care for patients and families [14]. Currently, incremental dialysis is the approach of reducing the dialysis dose by reduction in treatment time, days, or efficiency of clearance. Difficulties with the application of incremental dialysis include monitoring the deteriorating contribution of Kru over time and the need for frequent re-assessment and adjustment of the dose of dialysis. In this review, we seek to describe the potential benefits and limitations of incremental dialysis and its possible application to the pediatric population.

Incremental dialysis

The concept of incremental dialysis was formally introduced by Mehrotra et al., in an editorial to the 1997 Kidney Disease Outcomes Quality Initiative (KDOQI) for Peritoneal Dialysis Adequacy where they advocated for using incremental dialysis to avoid morbidity associated with delayed start of dialysis [15]. In practice, incremental dialysis has been implemented when resources were scarce and allowance for more frequent dialysis was limited [16]. In 1997, NKF-DOQI Clinical Practice Guidelines on peritoneal dialysis included residual kidney function in adequacy calculation for peritoneal dialysis thereby setting the precedent by which it has continued to be considered an important contributor towards providing adequate dialysis, or urea clearance, for those on peritoneal dialysis [17]. Although incremental dialysis has been more widely accepted in peritoneal dialysis patients, it has been curbed among those on hemodialysis based on accepted adequacy targets largely excluding residual kidney function.

Available studies in adult patients help demonstrate potential benefits and limitations of incremental dialysis. Obi et al., in 2016, compared patients initiating dialysis on an incremental dialysis regimen (2 times per week for at least 6 continuous weeks) to cohort-matched control initiating a conventional (3 times per week) regimen [18]. The incremental dialysis cohort had a greater Kru at baseline and demonstrated a slower decline in Kru and urine volume. One-year survival was similar overall, although when stratified by Kru and urine volume, incremental hemodialysis was associated with increased risk of death among patients with insignificant baseline Kru or urine volume. This risk was not seen among those with significant baseline Kru or urine volume. In contrast, an observational study from the Korean Clinical Research Center Registry [19] found that the twice-weekly cohort with residual kidney function had an adjusted mortality rate fourfold higher than the thrice-weekly cohort with residual kidney function. However, these results were confounded due to higher utilization rate of catheters and low flux dialyzers in the twice-weekly group. The twice-weekly cohort also had the greatest decline in normalized protein catabolic rate raising the question of potential nutritional deterioration with less intense dialysis. In follow-up, Wang et al. demonstrated similar risk of death between twice- and thrice-weekly matched incident hemodialysis patients when stratified by nutritional status [20]. Matthew et al. [21] compared survival among a cohort of conventional, incremental, and frequent HD patients; mortality was not different in the incremental cohort when compared to the conventional group. The frequent dialysis cohort, on the other hand, had increased mortality compared to the conventional HD cohort. Bieber et al. evaluated health-related quality of life (HRQoL) in a sub-cohort in China of the Dialysis Outcomes and Practice Pattern Study and found similar HRQoL scores among patients receiving twice-weekly when compared to those receiving thrice-weekly dialysis treatments [22].

A retrospective study from a single center in Switzerland compared mortality and hospitalization among 313 incident dialysis patients who initiated dialysis either with incremental hemodialysis ($n=68$), conventional hemodialysis ($n=166$), or peritoneal dialysis ($n=79$) from 01/2013 to 12/2020 [23]. To be a candidate for incremental hemodialysis, the patient had to produce > 500 ml/day of urine, have Kru > 2 ml/min, and limit interdialytic weight gain to < 2.5 kg. Those patients who met and maintained these criteria for incremental dialysis received 3 h of hemodialysis, twice weekly. Those on incremental hemodialysis had better survival (hazard ratio 0.49, 95% confidence interval 0.26–0.93; $p=0.029$) as compared to conventional hemodialysis and peritoneal dialysis. Hospitalization at 1 year was higher in the conventional hemodialysis group as compared to peritoneal dialysis and incremental hemodialysis. There was no difference in mortality between conventional hemodialysis and peritoneal dialysis. The rate of persistence of incremental dialysis at 1-year follow-up was 28.8%. Compared to the peritoneal dialysis cohort, the incremental dialysis group had similar urine output at 1 year, but a higher rate of decline from baseline.

Two systematic reviews and meta-analyses have been performed comparing incremental versus conventional dialysis. Garofalo et al. performed a systematic review and meta-analysis of cohort studies in adults with advanced chronic kidney disease initiating incremental hemodialysis and peritoneal dialysis to evaluate all-cause mortality, loss of residual kidney function, and time to full dialysis prescription [24]. Twenty-two studies were analyzed: 15 in HD and 7 in PD. Patients treated with an incremental modality did not show a higher risk of all-cause mortality when compared to those receiving full-dose dialysis. Kru preservation was higher in those receiving an incremental modality with an overall loss of residual kidney function 0.13 ml/min/month

in those receiving incremental dialysis compared to 0.74 ml/min/month in those receiving full-dose dialysis. The overall mean time to full-dose dialysis was 12.1 months with no significant difference in timing between those receiving incremental hemodialysis and incremental peritoneal dialysis. Furthermore, fewer complications were noted in those receiving incremental dialysis with improved survival of vascular access and lower peritonitis rates. Caton et al. [25] performed a systematic review and meta-analysis evaluating the safety, efficacy, and cost-effectiveness of incremental hemodialysis. They included 26 cohort studies and two randomized controlled trials with sample size ranging from 48 to 50,596 patients. They found no difference in mortality. The cohort studies suggested similar hospitalization rates but reduced loss of Kru in the incremental dialysis group, while the randomized control trials suggested lower hospitalization rates but no difference in preservation of Kru. The meta-analysis did not find a difference in HRQoL assessment scores between the incremental and conventional groups.

Recently, two randomized control feasibility trials in adults have been published to help guide larger, more definitive studies. The first, a multicenter randomized control trial with four participating centers in the UK, randomized 29 incident hemodialysis patients to incremental dialysis and 26 to conventional [26]. The incremental dialysis group received 2 weekly treatments of 3.5 to 4 h with a goal standard (Std) Kt/V > 2 with incorporation of Kru. The conventional arm received traditional 3 sessions per week of 3.5 to 4 h with goal Std Kt/V > 2; Kru in the conventional group was not measured. Minimum Kru of 3 ml/min/1.73 m^2 was required for inclusion into the incremental group, and monthly interdialytic urine collections were performed throughout the study. Hospitalizations and other serious adverse events such as vascular access events, extracellular volume overload, and cardiovascular events were significantly lower in the incremental dialysis group. The incremental dialysis group had lower serum bicarbonate levels and required more phosphate binders, though only the difference in serum bicarbonate level reached statistical significance. There was no difference between the groups regarding preservation of Kru at 6 months, defined either as Kru > 3 or > 2 ml/min/1.73 m^2. HRQoL assessments performed using six various tools demonstrated no difference. The second multicenter study from the USA performed a 1:1 randomization of patients with resultant 23 patients randomized into the incremental dialysis group and 25 into the conventional dialysis group [27]. Inclusion criteria for the incremental group included eGFR > 5 ml/min/1.73 m^2 and urine volume of > 500 ml/day. Incremental dialysis group received 6 weeks of twice-weekly dialysis with addition of loop diuretics; 39% received oral bicarbonate supplementation and 17% received patiromer. After 6 weeks, the incremental group received thrice-weekly dialysis. The conventional dialysis group received thrice-weekly dialysis from the onset. Baseline Kru > 2 ml/min was noted in 86% and 88% in the incremental and conventional groups respectively. Both groups had decline in urine volume at 6- and 12-week post randomization, but at 24-week post randomization, the incremental dialysis group demonstrated increase in urine volume by 22.8% and increased Kru by 12.4% as measured by combined urine clearance of urea and creatinine. At 24 weeks, the conventional group saw a reduction in urine volume and Kru by 28.2% and 45.5% respectively.

These two randomized control trials demonstrate that a larger definitive study is feasible and safe. Currently, there are few pending studies in adults planning to investigate potential benefits of incremental dialysis. A multicenter randomized trial (NCT03239808) plans to include 152 incident patients with Kru > 4 ml/min/1.73 m^2 based on urea clearance with the incremental group starting with once-weekly hemodialysis and increasing frequency per protocol. The primary objective is mortality and secondary outcomes of morbidity and quality of life assessments. A second multicenter randomized control trial (NCT03302546) plans to compare twice-weekly hemodialysis versus thrice weekly and measure preservation of Kru, mortality, and quality of life among 88 incident dialysis patients who can maintain a Kru > 2.5 ml/min/1.73 m^2 [28]. A larger study is planning to enroll 372 adult participants who produce at least 500 ml of urine per day from Australia, New Zealand, and Canada, comparing twice-weekly hemodialysis versus thrice weekly among incident patients with the primary outcome of HRQoL and secondary outcomes of morbidity and mortality (NCT04932148). Similar studies are planned among 252 veterans initiating hemodialysis (NCT05465044) and 116 participants across Europe (NCT04360694).

Together, these studies demonstrate that incremental dialysis does not increase the risk for mortality for incident dialysis patients who have significant Kru and urine production. Incremental dialysis may reduce morbidity such as hospitalization and access-related complications, but study results are mixed. Rate of decline of Kru and urine production may be slowed with incremental dialysis. Based on available data, HRQoL scores are likely not improved with incremental dialysis. The Korean experience also provides caution on potentially jeopardizing nutrition. The pending larger multicenter studies hopefully will shed more light on the benefits and risks of incremental dialysis. To date, there are no studies in the pediatric population investigating safety and benefits of incremental hemodialysis.

Optimal dialysis and pediatric consideration of incremental hemodialysis

For children and their caregivers, optimal dialysis includes more than just providing adequate clearance. Optimal dialysis allows for adequate growth, good metabolic control

without strict limitation in dietary choices, controlled blood pressure with maintenance of euvolemia, reduction in medication burden, preservation of quality of life with adequate energy to participate in daily activities, and minimization of morbidity from infection, access dysfunction, and caregiver burden [29, 30] (Fig. 1). Undoubtedly, preservation of Kru and urine volume will aid in achieving optimal dialysis. Frequently, home-based peritoneal dialysis is the preferred modality for children with advanced chronic kidney disease requiring dialysis and can address a majority if not all the factors key in providing optimal dialysis. Furthermore, it is not uncommon for peritoneal dialysis prescriptions to be adjusted to provide adequate clearance while accounting for Kru. In a certain subset of incident pediatric dialysis patients with significant Kru and urine output, incremental hemodialysis may be beneficial with a similar goal of promoting the child's growth and development. Implementation of incremental dialysis must not, however, come at the expense of the child's nutritional and caloric delivery.

Potential benefits of incremental hemodialysis in children

Major benefits of incremental dialysis include a reduced caregiver burden with allowance for increased participation in developmentally appropriate activities and improved school attendance with reduced frequency of dialytic treatments. These challenges and/or caregiver burden with dialysis initiation have been well described [31-33]. Given the experience in adults as described earlier, it cannot be assumed that implementation of incremental dialysis would result in improvement in HRQoL metrics.

Like adults, children would likely experience reduced access-related complications and preservation of Kru, though this hypothesis needs testing. They may have less medication burden with initiation of kidney replacement therapy. The cost to the dialysis center and burden on limited resources such as trained pediatric dialysis nurses may also be reduced.

Potential risks with incremental hemodialysis in children

Specific challenges for the pediatric nephrologist include ease of measuring urine volume and Kru among children, particularly those who are in diapers. Monthly assessment of Kru and urine output, in general, can be challenging. Methods to measure Kru using serum proteins such as beta-2-microglobulin have been studied but have not been validated in children and are not widely available clinically [34]. Delivery of adequate nutrition for growth and the preservation of euvolemia in children to meet their nutritional needs pose additional challenges. Application of incremental dialysis for adults often requires protein restriction [33, 35] which should never be recommended in growing children. However, the introduction of additional clearance may assist with management of the protein load if being limited to delay initiation of dialysis.

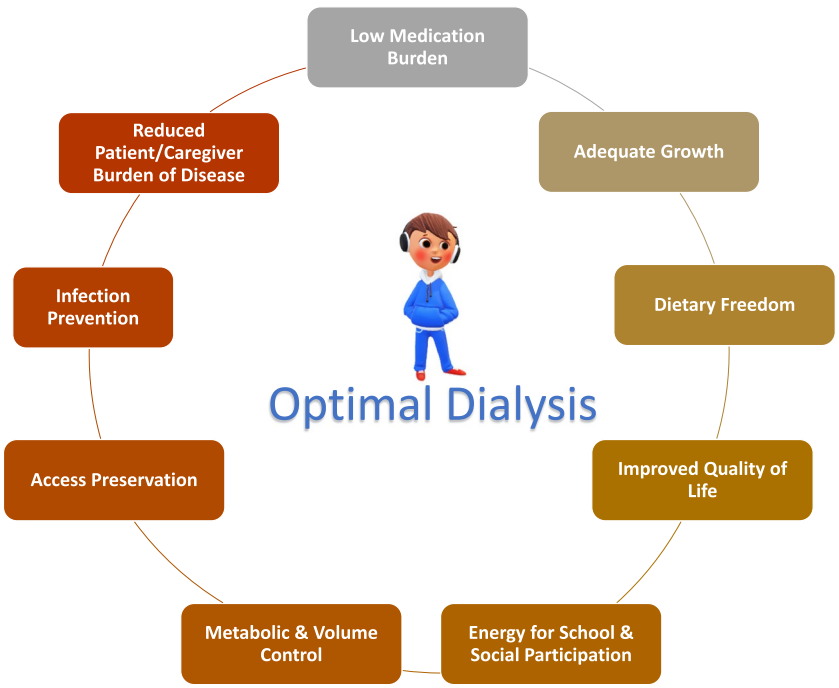

Fig. 1 Optimal dialysis

Criteria for consideration of incremental hemodialysis in children

Incremental dialysis can be considered for children who have advanced chronic kidney disease whose conservative management limits delivery of adequate nutrition and therefore growth. These children must have significant Kru and urine production. Furthermore, monthly monitoring of Kru and assessment of nutritional parameters would be paramount to prevent deterioration of health due to underdialysis. Patient and caregiver engagement would also be important as the dose and frequency of dialysis will need to be adjusted frequently. Thus, selection of appropriate patients for consideration would be crucial.

Rhee et al. and Gedney and Kalantar-Zadeh [36, 37] have outlined incremental dialysis protocols for adults with a focus on preservation of residual kidney function while recognizing the unique needs of the individual patient. These protocols include reduced days of dialysis treatments, shorter treatment times, or reduced daily dialysate solution volumes. The personalized approach considers the comprehensive needs of a patient, including medical history (residual kidney function, volume status, nutritional status), lifestyle factors, environment, and personal beliefs/preferences. They have proposed 10 clinical criteria to help identify suitable adult patients for incremental dialysis based on recommendations from the 1997 KDOQI Peritoneal Dialysis Work Group and the European Best Practice Guidelines Expert Group on Hemodialysis [14, 37]. These criteria focus on ensuring appropriate metabolic and volume control while achieving and maintaining good quality of life and allude to the need for close monitoring of Kru (Table 1). We use these criteria as a guide to propose pediatric criteria for incremental dialysis.

For adults, significant Kru is generally defined as greater than 2–3 ml/min and urine output of 500 ml/day. For children, depending on their muscle mass and body surface area, the amount of Kru and daily urine volume needed for metabolic balance and euvolemia will differ. We therefore would recommend a combined Std Kt/V > 2.3. This is in line with targets set by KDOQI 2015 recommendations and allows the potential underestimation of volume of distribution of urea in children resulting in overestimation of single pool Kt/V [5]. Formulas for estimating Std Kt/V with incorporation of Kru are described in the appendix to guideline 3 in the KDOQI Clinical Practice Guideline for Hemodialysis Adequacy: 2015 Update [5]. The urine volume would have to be sufficient to maintain less than 4% fluid gain within the interdialytic period to reduce risk of cardiovascular morbidity [38]. Accordingly, the child should be able to achieve and

Table 1 Proposed pediatric criteria for incremental hemodialysis with comparison of adult criteria

Proposed adult criteria for twice-weekly HD [14]	Proposed pediatric criteria for hemodialysis treatment adjustment
Good residual kidney function with urine output, 0.5 l/d	Standard combined Kt/V > 2.3
Limited fluid retention between 2 consecutive HD treatments with fluid gain, 2.5 kg (or 5% of ideal dry weight) without HD for 3–4 d	Limited fluid retention. Diuretic responsive with < 4% fluid gain between 2 consecutive HD treatments or %fluid gain, in which removal does not result in intradialytic hypotension, discomfort, or uncontrolled hypertension
Limited or readily manageable cardiovascular or pulmonary symptoms without clinically significant fluid overload	Home blood pressures < 90% based on auscultatory measurement and/or < 50% mean arterial pressure by ambulatory blood pressure measurement without evidence of left ventricular hypertrophy
Suitable body size relative to residual kidney function; patients with larger body size may be suitable for 2 ×/wk HD if not hypercatabolic	Able to maintain anabolic state. Acceptable weight gain and growth with the addition of growth hormone
Hyperkalemia (K > 5.5 mEq/l) is infrequent or readily manageable	Agree
Hyperphosphatemia (P > 5.5 mg/dl) is infrequent or readily manageable	Hyperphosphatemia is infrequent or readily manageable. PTH < 500 with medical management
Good nutritional status without florid hypercatabolic state	Agree, without need for protein restriction; continued linear growth with use of growth hormone (if appropriate)
Lack of profound anemia (Hb > 8 g/dl) and appropriate responsiveness to anemia therapy	Agree, with the caveat of targeting Hb > 9 g/dl
Infrequent hospitalization and easily manageable co-morbid conditions	Agree
Satisfactory health-related quality of life	Agree. In addition, satisfactory school participation, energy level, and appetite without symptomatic uremia
Additional proposed pediatric-specific criteria	
Unable to receive home peritoneal dialysis	
Non-glomerular etiology of chronic kidney disease	
Nutrition optimization aided by initiation of dialysis	
Parental commitment for frequent reassessment and dose adjustment	

maintain normotension. Most importantly, the child should also be able to achieve and maintain an anabolic state with optimization of growth and development with preservation of metabolic balance, including normal potassium and phosphorus levels, and delivery of appropriate calories, protein, and macro- and micronutrients. Repeated assessment, occurring at least monthly, would be key to therapy initiation and continuation to ensure that these criteria can be maintained. However, to truly assess outcomes, benefit, and safety of incremental hemodialysis in a subset of children, further studies in children specifically are needed.

Conclusion

Preservation of Kru and urine volume are key drivers associated with improved outcomes for patients with advanced chronic kidney disease on dialysis. Timing of initiation of dialysis remains dynamic, driven by multiple different factors. An incremental dialysis approach to initiation of kidney replacement therapy offers a methodology to preserve Kru and urine volume while allowing for manipulation of the dialysis prescription to meet a patient's individual needs with the goal to promote optimal health. Currently, incremental dialysis is practiced more with peritoneal dialysis as incorporation of Kru into the total weekly calculation is standard of care. Application to pediatrics should be considered in certain subsets of children with recognition of the need for frequent reassessment and adjustment to ensure the prescription meets all the child's needs for continued growth and development.

Declarations

Conflict of interest Raj Munshi has no conflict of interest. Sarah J. Swartz is a consultant/speaker for Fresenius Medical Care North America Jul 2021 through Dec 2021 to promote COVID vaccines in pediatrics.

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