The Decision to Initiate Dialysis in a Pediatric Patient

6

Larry A. Greenbaum and Franz Schaefer

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Overview

The initiation of chronic dialysis in a child is a dramatic event for the patient and family. Dialysis begins a new and often frightening stage of the child's medical care. The urgent need to begin dialysis is obvious in some instances, such as after bilateral nephrectomy or in the child with uremic pericarditis. These are absolute indications for initiating dialysis. In other patients the timing of dialysis initiation is less clear. The pediatric nephrologist integrates a great deal of information – laboratory data, clinical impressions, and psychosocial issues – in order to reach a decision regarding the timing of dialysis initiation. An assessment of renal function is usually a critical part of this process. In addition, a variety of clinical and laboratory findings are relative indications for commencing chronic dialysis. Some of these relative indications can be managed with medications and dietary counseling, but this approach is not always successful, necessitating the initiation of dialysis.

In the absence of absolute indications, there is no consensus on the appropriate timing of dialysis initiation. There is considerable debate regarding the merits of "early" initiation of dialysis in adults. The data needed to address this issue in children is nonexistent and the debate is complicated in children by issues such as growth, psychosocial factors, an impending kidney transplant, and the need for a lifetime of renal replacement therapy.

Children need a systematic plan of monitoring prior to dialysis initiation. Along with optimizing medical care, this allows the early identification of indications for dialysis. Some relative indications for dialysis may be amenable to medical management. For the child who will soon need dialysis, access and training needs can be anticipated, potentially avoiding unnecessary morbidity and expense from emergency initiation of dialysis.

L.A. Greenbaum, MD, PhD (✉)
Department of Pediatrics, Emory University
and Children's Healthcare of Atlanta, Atlanta, GA, USA
e-mail: lgreen6@emory.edu

F. Schaefer, MD
Pediatric Nephrology Division, Heidelberg University
Hospital, Heidelberg, Germany

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Methodology for Measuring Renal Function

Assessment of a patient's renal function is useful for determining when to initiate dialysis. In this context, renal function is usually defined as the patient's glomerular filtration rate (GFR). This purposely ignores other aspects of kidney function, such as erythropoietin production and synthesis of calcitriol, because dialysis does not replace these functions. GFR provides an estimate of functioning nephrons, but there are inherent limitations. First, there is an increase in single nephron GFR in chronic renal failure; this allows GFR to be maintained at a higher level than the reduction in functioning nephrons would dictate [1]. GFR may therefore overestimate the functional renal mass. However, for decisions about dialysis initiation this is of limited importance since it is GFR that dictates the need for dialysis. The second issue is that GFR may be transiently affected by a variety of factors other than the intrinsic renal disease. For example, intravascular volume depletion, nonsteroidal anti-inflammatory drugs, and antihypertensive therapy, especially with angiotensin-converting-enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), may decrease GFR. In such instances, a fall in GFR should be interpreted cautiously. A potentially reversible process warrants a repeat measurement of kidney function after the elimination of the underlying cause of the decrease in the GFR.

The gold standard for measuring GFR is inulin clearance, but this technique is usually only available in a research setting and is impractical clinically. Inulin is ideal for measuring GFR because it is freely filtered at the glomerulus and there is no tubular reabsorption or secretion.

Alternatives to inulin for measuring GFR include radioisotope markers, such as chromium 51-EDTA, iothalamate sodium I^{125} and technetium 99-DTPA [2], and the contrast agent iohexol [3]. These techniques are expensive and require multiple blood draws over 3–4 h, making them less than ideal for frequent monitoring. There is usually a good correlation between inulin clearance and the GFR estimated by radioisotopes, although some studies indicate that the accuracy decreases at low GFR [4]. Single-sample methods, while more convenient, are especially problematic at low GFR [5].

Creatinine clearance (CrCl) is a widely used approach for estimating GFR. Like inulin, creatinine is freely filtered at the glomerulus, but, unlike inulin, there is secretion of creatinine by the proximal tubule. This causes CrCl to overestimate GFR. The effect of creatinine secretion is fairly small at a normal GFR, causing a 5–10% overestimation of GFR. The relative impact of creatinine secretion increases as GFR decreases, leading to a more significant overestimation of GFR. In one study of adults with a mean GFR of 22 mL/min, the CrCl was close to double the inulin clearance [6]. Further, a variety of factors influence creatinine secretion. Creatinine secretion is lower in patients with polycystic kidney disease and higher in patients with glomerular disease [7]. Some medications, such as cimetidine, trimethoprim, and some fibrates, decrease creatinine secretion. Advanced liver disease may increase creatinine secretion. Finally, a valid calculation of CrCl requires an accurately timed urine collection. All of these factors limit the accuracy of CrCl, especially at the low levels of GFR when decisions regarding dialysis initiation are necessary.

Despite its limitations, CrCl is an easy and inexpensive surrogate for GFR. CrCl is calculated via the following equation:

$$\mathrm{CrCl} = \frac{U_{vol} \times U_{Cr} \times 1.73}{\mathrm{Min} \times S_{Cr} \times \mathrm{BSA}} \qquad (6.1)$$

where CrCl = creatinine clearance (mL/min/1.73 m^2), U_{vol} = Urine volume (mL), U_{Cr} = urine creatinine concentration (mg/dL), Min = collection period in minutes (1,440 for 24 h), S_{Cr} = serum creatinine (mg/dL), BSA = body surface area in m^2.

A CrCl requires a timed urine collection, usually 12 or 24 h, necessitating bladder catheterization in the absence of urinary continence. This is a significant impediment to repeat measurements in children.

An alternative to a standard CrCl is to administer cimetidine to the patient prior to the study.

Cimetidine, by decreasing tubular secretion of creatinine, improves the accuracy of the CrCl in predicting GFR. One study of 53 children showed that a 2 h cimetidine protocol resulted in a CrCl that closely approximated a simultaneous inulin clearance [8].

Urea clearance underestimates GFR because of tubular reabsorption of urea. The calculation of urea clearance requires a timed urine collection and a serum urea concentration:

$$C_{Urea} = \frac{U_{vol} \times U_{urea} \times 1.73}{Min \times S_{urea} \times BSA} \quad (6.2)$$

where C_{urea} = Urea clearance (mL/min/1.73 m^2), U_{vol} = Urine volume (mL), U_{urea} = urine urea concentration (mg/dL), Min = collection period in minutes (1,440 for 24 h), S_{urea} = serum urea concentration (mg/dL), BSA = body surface area in m^2.

At low levels of GFR, the percentage of filtered urea that is reabsorbed is approximately equal to the percentage of filtered creatinine that is secreted. Therefore, the mean of CrCl and urea clearance is another way of estimating GFR and in adults is quite accurate at low levels of GFR [9, 10].

In children, an estimate of GFR may be calculated from the serum creatinine using an equation [11]. This equation uses patient height and a constant, which may vary based on age and gender to attempt to correct for differences in muscle mass:

$$GFR = \frac{\text{Height (cm)} \times k}{S_{Cr}} \quad (6.3)$$

where GFR = glomerular filtration rate (mL/min/1.73 m^2) and S_{Cr} = serum creatinine concentration (mg/dL). The traditional Schwartz equation uses the following constants: k = 0.55 for boys 2–12 and girls 2–18 years; k = 0.70 for boys 13–18 years; k = 0.45 for children <2 years; k = 0.33 for infants <2.5 kg.

More recently, a study of children with CKD recommends a constant of 0.413 irrespective of age and gender [12]. The decrease in the constant is predominantly secondary to changes in the methodology for measuring creatinine, with the most recent constant based on the enzymatic method for measuring creatinine. The older constant was derived using the Jaffe method. Hence, it is critical to be aware of the laboratory methodology that is being utilized when applying these formulas.

The accuracy of these formulas has been questioned by a number of studies [13–16]. The formulas appear especially problematic in malnourished children and at the low levels of renal function where decisions regarding dialysis initiation need to be made. There are a variety of factors that decrease the accuracy of using formulas that depend on the serum creatinine concentration to estimate GFR. The serum creatinine concentration depends on the balance between creatinine generation and excretion. Creatinine is largely derived from breakdown of muscle creatine and thus creatinine generation is proportional to muscle mass, which varies greatly in children, mostly related to size, but also due to gender, age, and individual differences. In adults there are racial differences in creatinine generation [17].

Children with uremia may lose muscle mass due to malnutrition, possibly reducing the rise in serum creatinine concentration. Spinal cord injury or amputation are other potential causes of a misleadingly low serum creatinine. During cooking, creatine in meat is converted to creatinine. Therefore, serum creatinine is partially influenced by the amount of dietary meat, which often decreases in renal insufficiency due to phosphorus restriction and anorexia. Extrarenal creatinine excretion increases in patients with chronic renal failure [18]. Moreover, tubular creatinine secretion increases as the GFR decreases [6]. Extrarenal excretion and tubular secretion blunt the increase in serum creatinine concentration that should occur as GFR decreases. As stressed above, medications and the specific disease causing chronic renal failure can affect creatinine secretion [7].

The serum protein cystatin C, an endogenous protein, is an alternative to creatinine for estimating GFR [19]. It is unclear whether cystatin C is superior to creatinine for estimating GFR in children, although the combination of cystatin C and creatinine may be used to create more accurate, albeit more complex equations for estimating GFR [12, 19, 20]. However, there is not a general

agreement on the correct constants to utilize for cystatin C estimates of GFR [12, 20, 21], perhaps partially due to differences in methodologies for measuring cystatin C. Additionally, cystatin C is not readily available and is more expensive than serum creatinine.

For adult patients, the Cockcroft–Gault formula is widely used to estimate GFR [22]. An alternative formula, based on data from the Modification of Diet in Renal Disease (MDRD) study, provides a more accurate method for estimating GFR in adults, although it requires fairly complex calculations [23]. These equations are of limited utility in children [24].

Dialysis adequacy is conventionally measured by calculating Kt/V for urea (Kt/V_{urea}) [25, 26]. Calculation of Kt/V_{urea} from residual kidney function is an alternative to estimates of GFR as a way of determining the need for dialysis. Calculation of Kt/V_{urea} requires a 24-h urine collection and serum urea concentration:

$$\text{Weekly } Kt/V_{urea} = \frac{U_{vol} \times U_{urea}}{V_{TBW} \times S_{urea}} \times 7 \qquad (6.4)$$

where U_{vol} = urine volume (liters/day), U_{urea} = urine urea concentration (mg/dL), S_{urea} = serum urea concentration (mg/dL), V_{TBW} is total body water (liters). Multiplication of the daily urea clearance by 7 calculates the weekly urea clearance. The KDOQI guidelines recommend estimating TBW using tables derived from a study of children receiving peritoneal dialysis [26, 27].

Kt/V_{urea} may be misleading in patients with malnutrition. Poor nutrition reduces patient weight and hence V_{TBW}, leading to an increase in Kt/V_{urea} and the impression that urea removal is better than it appears. For patients on peritoneal dialysis, the KDOQI guidelines recommend calculation of V_{TBW} using ideal weight as opposed to actual weight [26]. This may be especially important in using Kt/V_{urea} as a guide to the decision to initiate dialysis since it is the patient with malnutrition who is postulated to receive the most benefit from dialysis initiation.

In predialysis patients the relationship between Kt/V_{urea} and CrCl is different than in patients receiving dialysis. This is because of tubular reabsorption of urea and the lower clearance of creatinine than urea by dialysis. Therefore, for the same CrCl, Kt/V_{urea} in predialysis patients is lower than in patients on dialysis [28]. In one study of adult predialysis patients, Kt/V_{urea} correlated better than CrCl with protein intake, a surrogate marker of nutritional status [28]. Yet, in another study in adults there was a good correlation between CrCl and dietary protein intake [29].

All of the different methodologies have drawbacks. There is no consensus on the method that best identifies the patient who needs to initiate dialysis. Different decisions occur depending on the method [30].

Predialysis Patient Monitoring

Systematic patient monitoring is necessary in children with chronic renal failure to minimize complications such as malnutrition, hypertension, renal osteodystrophy, and poor growth. In addition, regular monitoring identifies children who have relative or absolute indications for starting dialysis. Anticipation of the need for dialysis permits nonemergent placement of a peritoneal dialysis catheter or creation of a vascular access for hemodialysis or performance of a preemptive kidney transplant. Table 6.1 outlines

Table 6.1 Evaluation schedule for children with chronic renal failure

Timing	Evaluation
At least every 3 months	Length/height, weight gain, head circumference in infants, blood pressure, acid–base status, electrolytes, creatinine, BUN, CBC, albumin, PTH, estimation of GFR
Every 6–12 months	Echocardiography, ABPM, hand X-ray, neurodevelopmental assessment in infants

Abbreviations: BUN, blood urea nitrogen; CBC, complete blood count; PTH, parathyroid hormone; ABPM, ambulatory blood pressure monitoring

the necessary components for monitoring children with a GFR < 30 mL/min/1.73 m^2.

Indications for Initiating Dialysis

Absolute Indications for Initiating Dialysis

A variety of signs and symptoms are absolute indications for dialysis initiation. These are manifestations of renal failure that cause significant morbidity and mortality. There is usually a dramatic or marked improvement with initiation of dialysis. An alternative explanation for the clinical finding should be considered, especially if the GFR is unexpectedly high or if dialysis does not produce improvement.

Neurologic consequences of uremia that are absolute indications for dialysis include encephalopathy, confusion, asterixis, seizures, myoclonus, and wrist or foot drop. Children should begin dialysis if there is hypertension that does not respond to antihypertensive therapy or pulmonary edema due to volume overload unresponsive to diuretics. Other absolute indications for starting dialysis are pericarditis, bleeding diathesis, and refractory nausea and emesis.

Bilateral nephrectomy, as may be necessary in some children with congenital nephrotic syndrome or autosomal recessive polycystic kidney disease, is an absolute indication for dialysis.

Beyond anuria, there is debate regarding the precise level of renal function, along with the methodology for measuring renal function, that is, an absolute indication for dialysis. In addition, there are recommendations that the presence of malnutrition lowers the threshold for dialysis initiation based on the level of renal function. Again, there is no consensus regarding the measurement of malnutrition, the degree of malnutrition that must be present, or the role of alternative strategies to alleviate malnutrition. We summarize in Sects. "Relative Indications for Initiating Dialysis" and "Timing of Elective Dialysis Initiation" the data and opinions regarding the level of renal function and the role of malnutrition as relative or absolute indications for dialysis initiation.

Relative Indications for Initiating Dialysis

Uremic Symptoms

While severe uremic symptoms are absolute indications for dialysis, less dramatic symptoms are relative indications. These include fatigue and weakness, cognitive dysfunction, decreased school performance, pruritus, depression, nausea, emesis, anorexia, restless leg syndrome, and poor sleep patterns. The persistence and severity of these symptoms are important criteria. This is especially true when evaluating gastrointestinal symptoms. Intractable emesis is an absolute indication for dialysis while occasional emesis, especially if there are no signs of malnutrition, may not require dialysis initiation.

Many of the symptoms that can be associated with uremia have alternative explanations. Medications may cause fatigue, depression, or nausea. Anemia, a correctable problem, may contribute to fatigue. Depression and poor school performance may be related to psychosocial issues. Comorbid conditions may also cause significant symptoms. Conversely, many patients with uremic symptoms may minimize or deny symptoms in an effort to avoid dialysis or because they perceive these symptoms, which may have developed quite gradually, as normal.

Hyperkalemia

Hyperkalemia is a potentially life-threatening complication of chronic renal failure [31]. As GFR decreases, the remaining nephrons compensate by increasing potassium excretion, but there is a linear relationship between GFR and the ability to excrete a potassium load [32–36]. Hyperkalemia usually does not become problematic until the GFR is less than 10–20 mL/min, unless potassium intake is excessive or excretion is reduced [33, 37]. Hyperkalemia develops at a higher GFR in adults and children with hyporeninemic hypoaldosteronism, which may also cause a type IV renal tubular acidosis [35, 38, 39]. Similarly, other patients have a decreased tubular responsiveness to aldosterone and this pseudohypoaldosteronism may cause hyperkalemia at higher levels of GFR [40–43]. These

patients may also have type IV renal tubular acidosis. Medications, especially ACE inhibitors, calcineurin inhibitors, and potassium sparing diuretics, are another important cause of reduced urinary potassium excretion.

Treatment of hyperkalemia in association with chronic renal failure relies on decreasing dietary potassium intake and increasing potassium excretion. In older children avoidance of foods with high potassium content can have a dramatic effect on potassium intake. Whereas in older children who are receiving liquid formula supplementation it is possible to select a formula with a low potassium content, the potassium content of standard infant formula does not vary greatly, limiting the effectiveness of formula selection. Low-potassium formulas adapted to the needs of children with advanced CKD are available in individual countries (e.g., Nefea, MetaX in Germany). It should be noted, that soy-based and elemental formulas are especially high in potassium. Human milk has lower potassium content than most formulas, while cow's milk has about twice the potassium content of most infant formulas. A reduction in the potassium delivery from infant formula is possible by fortifying the formula with sugar (e.g., Polycose) and/or fat. With a higher caloric content, less formula, and hence less potassium, is needed to provide adequate calories. Alternatively, preparing formula with deionized water decreases the potassium content [44].

Increasing potassium excretion can help ameliorate the hyperkalemia of chronic renal failure. Loop diuretics increase urinary potassium excretion; adequate sodium intake is necessary for maximum effectiveness. Discontinuation of medications that decrease urinary potassium excretion, such as ACE inhibitors, angiotensin II blockers, nonsteroidal anti-inflammatory drugs, or potassium sparing diuretics, can have a significant effect on the serum potassium level [45, 46]. Although not usually a significant mechanism of potassium excretion, stool potassium losses become more important as renal function declines [47]. Constipation should be treated since it may decrease stool potassium losses. Sodium polystyrene sulfonate (Kayexalate®), an exchange resin, binds potassium in the gastrointestinal tract, significantly increasing stool potassium losses [48]. Typically given orally or via a G-tube, sodium polystyrene sulfonate is very effective in treating hyperkalemia in children with chronic renal failure. Pretreatment of formula with sodium polystyrene sulfonate is effective, but may cause constipation and problems with other electrolytes, especially increased formula sodium content [44, 49, 50].

Because of the effectiveness of dietary and medical intervention, initiation of chronic dialysis is seldom necessary solely to manage hyperkalemia. Nevertheless, repeated episodes of severe hyperkalemia may be considered an absolute indication for dialysis. Poor adherence to dietary restriction or medication usually contributes to refractory hyperkalemia. Hemodialysis and peritoneal dialysis are quite effective at removing body potassium, although dietary restriction, and occasionally medical management, is usually still necessary.

Hyperphosphatemia

A decrease in filtered phosphate parallels the decrease in GFR in chronic renal failure. With mild to moderate renal insufficiency, an increase in the fractional excretion of phosphate by the remaining nephrons initially compensates, permitting the serum phosphorus to remain normal [51]. As the GFR falls, compensation is inadequate and hyperphosphatemia ensues, typically at CKD stages 2 or 3 [52–54]. Hyperphosphatemia causes secondary hyperparathyroidism by suppressing 1,25-dihydroxyvitamin D production and calcium levels and through direct stimulation of PTH secretion [55–57]. Correction of hyperphosphatemia is essential for controlling secondary hyperparathyroidism. In addition, hyperphosphatemia may elevate the serum calcium-phosphorus product and contribute to vascular calcifications [57–59]. In adult patients with CKD, serum phosphate levels predict mortality and progression of CKD [58–60].

The management of hyperphosphatemia in chronic renal failure depends on a reduction in phosphate intake by a combination of dietary phosphate restriction and the use of phosphate binders [61]. Early in renal failure, before hyperphosphatemia develops, reduction in phosphate intake helps to control secondary hyperparathyroidism

[51, 54, 62–64]. For infants, dietary phosphate restriction is facilitated by the availability of formula with a low phosphate concentration (e.g., Similac PM 60/40). Liquid nutritional supplements with a low phosphate content are also available for older children. As renal function declines, dietary restriction, because of nutritional constraints and limitations of food palatability, is often inadequate to control hyperphosphatemia, necessitating the use of phosphate binders. Calcium carbonate is an effective phosphate binder in children with chronic renal failure, although excessive use may cause hypercalcemia and contribute to systemic calcifications [65]. Sevelamer, a calcium-free phosphate-binding agent, has been effectively utilized to control hyperphosphatemia in children [66], and has been shown to slow the rate of vascular calcifications in adult patients [67]. However, all available phosphate binders must be administered in large doses (several grams per day) to be effective; the need to swallow large numbers of large-sized tablets or capsules limits the acceptability of medical therapy in children. Hence, poor adherence to dietary and medical therapy is the most important obstacle to control hyperphosphatemia.

While dialysis therapy removes phosphate, it is almost never adequate to control hyperphosphatemia by itself. There is a continued need for dietary restriction and phosphate binders. The initiation of dialysis because of refractory hyperphosphatemia is seldom effective at controlling hyperphosphatemia since the underlying problem, nonadherence to therapy, is still present. Hence, isolated hyperphosphatemia is seldom the only indication for dialysis, unless there is a belief that the combination of dialytic phosphate removal and improved adherence, perhaps due to the more regimented medical care required by dialysis, will facilitate the control of hyperphosphatemia. The presence of refractory hyperparathyroidism further lowers the threshold for dialysis initiation.

Malnutrition

Uremia causes symptoms such as emesis and anorexia that may prevent adequate caloric intake. In adults and children, dietary protein and energy intake declines as the GFR decreases [29, 68–71]. In children, this may adversely affect growth [43]. Further, studies in adult patients show an association between malnutrition when starting dialysis and decreased patient survival [29, 72–81]. Nutritional parameters improve in adult patients after initiation of dialysis [69, 71, 82–87]. When looking at body fat as an index of nutritional status, poor nutritional status at the start of dialysis was associated with a greater increase in body fat [84]. In other studies, there was a positive correlation between the nutritional status at the start of dialysis and the follow-up nutritional status, suggesting that dialysis may not completely compensate for poor nutrition at dialysis initiation [83, 87].

The improved survival with increased dialysis dose, the mortality risk associated with malnutrition, and the improvement in nutritional status with dialysis are the basis for recommendations to initiate dialysis therapy when a patient has advanced chronic renal failure and malnutrition [26, 88, 89]. Yet, there are no prospective studies demonstrating that the early initiation of dialysis improves outcome. An alternative solution to the combination of malnutrition and advanced renal failure is the initiation of aggressive dietary intervention, which has proven successful in some adult patients [90, 91]. This approach, using severe restriction of dietary protein, is not utilized in children due to concerns about the effects of protein restriction on growth and development. Alternatively, aggressive nutritional supplementation, possibly using a gastrostomy tube, may reverse malnutrition in some children without the need for dialysis [92, 93].

There is no one ideal marker of malnutrition. Signs of poor nutrition in children with chronic renal failure may include inadequate weight gain, poor linear growth, and a low serum albumin. A low serum albumin is misleading in the child with nephrotic syndrome and significant urinary protein losses. Other indications of malnutrition include a low serum prealbumin, transferrin or cholesterol, inadequate dietary protein, decreased creatinine excretion, and a loss of muscle mass. If indices of malnutrition cannot be improved by conservative interventions, then the child with advanced chronic renal failure should begin dialysis.

Growth Failure

Growth retardation is a common complication of chronic renal failure in children [94]. The causes of "uremic" growth failure include malnutrition (most markedly in infants), electrolyte losses and fluid losses (in children with hypo/dysplastic kidney disorders), metabolic acidosis, osteodystrophy, anemia, and, most importantly beyond infancy, impaired function of the somatotropic hormone axis. Electrolyte and bicarbonate losses can usually be managed conservatively, with favorable effects on growth rates. Forced feeding usually improves the nutritional status, but linear growth may not respond to nutritional recovery once growth failure is established [95]. In children with stable predialytic chronic renal failure, recombinant growth hormone therapy is indicated. The efficacy of this therapy strongly depends on residual renal function, mandating a timely start of treatment [96,97]. Unresponsiveness to growth hormone may be considered as an argument to start dialysis, although improved growth rates are not consistently observed after initiation of standard peritoneal or hemodialysis [98]. Recently, short daily hemodiafiltration was demonstrated to improve responsiveness to growth hormone leading to remarkable, complete catch-up growth [99]. Hence, the availability of an intense hemodialysis program may be an argument to start dialysis in a child with growth hormone resistant growth failure.

Timing of Elective Dialysis Initiation

The level of renal function that is an absolute indication for initiating dialysis in children is uncertain. There is a paucity of pediatric data and the adult literature is fraught with conflicting conclusions and opinions [100–108]. The debate is complicated by uncertainty regarding the best methodology for evaluating residual renal function (see Sect. "Methodology for Measuring Renal Function"). The IDEAL study directly addressed this question in adults [109]. Patients were randomized to dialysis initiation at an estimated GFR of 10–15 mL/min/1.73 m^2 or at an estimated GFR of 5–7 mL/min. The late-start group began dialysis close to 6 months later than the early-start group, but there was no difference in mortality or other adverse events between the two groups. Hence, planned early initiation of dialysis was not associated with a clinical benefit [109].

A European multicenter study reported the estimated GFR at initiation of renal replacement therapy (RRT) in a large cohort of pediatric patients [110]. The median estimated GFR was10.4 mL/min/1.73 m^2, with the small percentage of the patients who received a preemptive transplant having a significantly higher estimated GFR at the time of transplant (13.5 mL/min/1.73 m^2). Variables associated with a lower estimated GFR at onset of RRT included younger age, female gender, and a short interval between the first visit to a pediatric nephrologist and commencement of RRT.

Consensus Statements Regarding Dialysis Initiation

The National Kidney Foundation's KDOQI guidelines recommend considering the risks and benefits of dialysis when a patient reaches stage 5 CKD (estimated GFR <15 mL/min/1.73 m^2), although dialysis at a higher GFR is an option if a specific indication is present (e.g., malnutrition or growth failure refractory to medical management) [25, 26]. Caring for Australasians with Renal Impairment (CARI) recommends starting dialysis when the GFR is below 6 mL/min/1.73 m^2, although earlier initiation should be considered if there is evidence of uremia or malnutrition when the GFR is below 10 mL/min/1.73 m^2 or even at higher GFRs if a specific indication is present [89].

The European guidelines recommend a threshold level of 6 mL/min/1.73 m^2, but that dialysis should be considered if the GFR is 8–10 mL/min/1.73 m^2 to avoid starting at a level less than 6 mL/min/1.73 m^2 [111]. The Canadian Society of Nephrology clinical practice guidelines recommend the initiation of dialysis when the GFR is less than 12 mL/min/1.73 m^2 and there is evidence of uremic symptoms or malnutrition [88]. A GFR less than 6 mL/min/1.73 m^2 is an absolute

indication for dialysis. The principal rationale for 6 mL/min/1.73 m^2 is the high likelihood, given the normal rate of loss of GFR in chronic renal failure, that an unacceptably low GFR will be present within 6 months [88].

Arguments for Early ("Timely") Initiation

This is based on the observation that adults who start dialysis with a lower GFR have increased morbidity and mortality [101, 112, 113]. This may be secondary to the effects of malnutrition since decreased residual renal function is associated with poor nutrition and poor nutrition when starting dialysis is associated with increased morbidity and mortality (see Sect. "Malnutrition"). Moreover, in the 1990s many adult patients initiated dialysis at a lower GFR than was recommended [28, 114, 115]. This led to the argument that more timely initiation of dialysis has the potential to lessen the high mortality in adult dialysis patients.

Since these observations, there has been a trend toward earlier initiation of dialysis in adults [106, 116]. In the United States, the percentage of patients starting dialysis with a GFR > 10 mL/min/1.73 m^2 increased from 25% to 54% between 1996 and 2005 [106]. This has been associated with observations suggesting that early initiation of dialysis may be harmful, with increasing mortality in patients who start early [103, 117]. However, this detrimental effect of early dialysis may be secondary to increased age and comorbidity in the patients who start early [104]. Older patients have had the most dramatic increase in early initiation of dialysis over the last decade [106]. Additionally, a lower serum creatinine, which results in a higher estimate of GFR, may also be explained by decreased muscle mass and poor nutritional status [117]. Hence, some patients with putative early initiation of dialysis may have a falsely elevated estimated GFR due to poor nutritional status, a well-defined risk factor for morbidity and mortality (see Sect. "Malnutrition"). This would create additional bias suggesting that early initiation of dialysis is harmful.

Arguments for Delayed Initiation

While a number of studies have shown a worse outcome in adults who have a lower GFR at dialysis initiation, there are a variety of biases that make interpretation difficult [101]. These include lead-time bias, referral time bias, and patient selection [88]. Lead-time bias refers to the fact that patients who start dialysis at lower GFR are further along in their disease than patients who start at a higher GFR. A fairer comparison is survival from a time when patients had the same GFR. After accounting for lead-time, two studies found no survival benefit for early dialysis initiation [107, 118]. Moreover, early initiation of dialysis may be associated with increased mortality [100, 105]. In adult patients, late referral to a nephrologist is a predictor of poor outcomes [119–124]. Such patients are more likely to have a lower GFR at dialysis initiation, again tending to bias the outcome against late initiation of dialysis. In addition, late referral patients are more likely to have a history of noncompliance with follow-up and more significant comorbid conditions [101].

Early initiation of dialysis exposes the patients to risks of complications from dialysis therapy, including peritonitis, irreversible loss of peritoneal function, access infections, and loss of large blood vessels for vascular access [125]. In one study of early initiation of peritoneal dialysis in adult patients, there were a significant number of complications [126]. These issues are especially important in children given the need for a lifetime of end-stage renal disease care. In addition, especially in the case of peritoneal dialysis, there is a risk of family and patient "burn-out" as the time on dialysis increases. Hemodialysis may prevent school attendance and certainly requires an extended amount of time at the dialysis unit. Many children feel "washed out" after completing hemodialysis, limiting the ability to complete homework or play with friends. Morning hypotension may prevent school attendance in children receiving peritoneal dialysis.

Residual renal function is associated with better outcomes in adults receiving dialysis [127, 128], and dialysis accelerates the loss of residual renal function [129]. This is more significant with

hemodialysis than continuous ambulatory peritoneal dialysis, both in adults and children [130–133]. The use of automated PD may [134, 135] or may not provoke a more rapid decline than classical CAPD [131, 136]. Of particular relevance to children, it appears that short, high-turnover NIPD may exert similarly detrimental effects on residual renal function as intermittent extracorporeal procedures.

While some children may bypass dialysis and receive a preemptive transplant, this exposes the child to the risks of long-term immunosuppression (infection and malignancy) and the growth stunting effects of corticosteroids. Moreover, early transplantation should, statistically, lead to earlier graft failure. These factors argue against overly aggressive use of preemptive transplantation.

In some children, dialysis may be delayed because a living-related transplant is imminent. This avoids the morbidity of dialysis initiation. In other cases, psychosocial issues may delay dialysis initiation. In both of these instances, the possible benefits of early initiation are counterbalanced by other factors.

Choice of Mode of Dialysis

Kidney transplantation is the optimal therapy for most adults and children with end-stage renal disease [137]. In many instances transplantation is not an immediate option because of the lack of a suitable donor. For some patients, psychosocial issues may need to be addressed before proceeding with transplantation.

The majority of adult patients receive treatment with hemodialysis. In pediatric patients, peritoneal dialysis is the more frequently used modality. There is debate in the adult literature regarding the optimal form of therapy. There are no randomized studies that properly address this issue. A number of nonrandomized studies show no difference in outcome, although other studies suggest an advantage for either hemodialysis or peritoneal dialysis [139–143]. Among adult patients, technique failure is more common with peritoneal dialysis [144, 145]. Selection bias has made it difficult to perform comparative studies of morbidity and mortality between peritoneal dialysis and hemodialysis in pediatric patients [146].

Peritoneal dialysis may be especially advantageous during the first 2 years of therapy [141, 147]. This may be related to the improved preservation of residual renal function with peritoneal dialysis [132, 133, 144]. In addition, the inability of peritoneal dialysis to match the weekly urea clearance of hemodialysis may be less of a problem when the patient has residual renal function, as is common during the first 2 years of therapy [143]. Finally, membrane failure may decrease the benefits of peritoneal dialysis after the first 2 years of dialysis [125]. Prolonged treatment with peritoneal dialysis may lead to membrane failure, which is associated with increased mortality [148, 149]. Moreover, a high transporter state in children on peritoneal dialysis is associated with poor growth [150]. The advantages of peritoneal dialysis during the first 2 years are especially relevant for children since they receive transplants sooner than adult patients due to the availability of living-related donors and higher priority on the cadaveric transplant list.

The adult literature supports the premise that the preferred mode of dialysis may depend on the patient population [142, 151, 152]. In children, peritoneal dialysis has a number of advantages. A home-based therapy is less disruptive with school and social activities. In infants, the performance of hemodialysis is associated with a significant risk for morbidity and mortality, especially if anuria is present [153]. Problems include difficulties with vascular access, refractory anemia, inadequate urea removal, and the risk of hemodynamic instability [153]. In addition, nutrition in infants is dependent on a high fluid intake, making it very difficult for thrice weekly hemodialysis to provide adequate fluid removal.

The choice of dialysis modality is based on a number of considerations. There are relative and absolute contraindications for both modalities (see Tables 6.2 and 6.3). Psychosocial considerations are quite important given the family commitment needed to make peritoneal dialysis

Table 6.2 Contraindications to hemodialysis in children

Absolute	Relative
Very small patients Lack of vascular access Contraindications to anticoagulation	Poorly controlled hypertension or hypertensive cardiomyopathy
Cardiovascular instability	Lack of proximity to a pediatric hemodialysis center

Table 6.3 Contraindications to peritoneal dialysis in children

Absolute	Relative
Omphalocele or gastroschisis	Impending abdominal surgery
Bladder exstrophy Diaphragmatic hernia	Impending living-related transplant
Peritoneal membrane failure	Lack of an appropriate caregiver

successful. Unless there are contraindications, peritoneal dialysis is the preferred modality for the majority of children, although both the family and the patient must be comfortable with the decision.

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