9 The Decision to Initiate Dialysis in Children and Adolescents

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Introduction

The initiation of chronic dialysis in a child is a dramatic event for the patient and family. There are absolute indications for initiating dialysis in some patients (e.g., bilateral nephrectomy, uremic pericarditis). In other patients, the reasons behind the timing of dialysis initiation are 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 kidney function is usually a critical part of this process. There is considerable debate regarding the merits of "early" initiation of dialysis in adults. The data needed to address this issue in children is sparse, 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.

Methodology for Measuring Kidney Function

Assessment of a patient's kidney function, usually defined as the patient's glomerular filtration rate (GFR), is useful for determining when to initiate dialysis. This purposely ignores other aspects of kidney function, such as erythropoietin production and synthesis of calcitriol, because dialysis does not replace these functions. However, GFR may be transiently affected by a variety of factors other than the intrinsic kidney disease. For example, intravascular volume depletion, nonsteroidal anti-inflammatory drugs, and antihypertensive therapy, especially angiotensin-converting enzyme (ACE) inhibitors or angiotensin II 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 eliminating the possible 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. Alternative exogenous substances for measuring GFR include chromium 51-labeled ethylenediaminetetraacetic acid (^{51}Cr-EDTA), diethylenetriaminepentaacetic acid (DTPA), iohexol, and iothalamate [1, 2].

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There is evidence for a good correlation between inulin clearance and some of these alternatives [3], although the accuracy may decrease in the setting of a low GFR [4, 5] and in patients with edema [6]. These techniques are expensive and require multiple blood draws over 3 to 4 hours, making them impractical for frequent monitoring. Single-sample methods, while more convenient, are especially problematic when the GFR is low [7].

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 the CrCl to overestimate GFR. The effect of creatinine secretion is 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 [8]. 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 [9]. 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:

$$\mathrm{CrCl} = \frac{U_{\mathrm{vol}} \times U_{\mathrm{Cr}} \times 1.73}{\mathrm{min} \times S_{\mathrm{Cr}} \times \mathrm{BSA}} \qquad (9.1)$$

where CrCl is the 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 (1440 for 24 hours); S_{Cr}, serum creatinine (mg/dL); and BSA, body surface area in m^2.

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

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; it is quite accurate at low levels of GFR in adults [10, 11].

In children, an estimated GFR (eGFR) may be calculated from the serum creatinine using an equation that uses patient height and a constant of 0.413 irrespective of age and gender [12]. The equation is referred to as the "CKiD creatinine equation" or the "modified Schwartz equation."

$$\mathrm{eGFR} = \frac{\mathrm{Height}\left(\mathrm{cm}\right) \times 0.413}{\mathrm{Scr}} \qquad (9.2)$$

This equation and subsequent referenced equations in this chapter are based on measuring creatinine using the enzymatic method traceable to isotope dilution mass spectrometry (IDMS traceable). A different constant was used for estimating GFR with an equation using the Jaffe method for determination of creatinine [13]. 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 [14, 15]. The formulas appear especially problematic in malnourished children and at the low levels of kidney function where decisions regarding dialysis initiation need to be made [15]. There are multiple factors that decrease the accuracy of 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. Thus, creatinine generation is proportional to muscle mass, which varies greatly in children and is mostly related to size, but also varies due to gender, age, and individual differences. In adults, there are racial differences in creatinine generation [16].

Children with uremia may lose muscle mass due to malnutrition, possibly reducing the rise in

serum creatinine concentration. Spinal cord injury and 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 kidney insufficiency due to phosphorus restriction and anorexia. Extrarenal creatinine excretion increases in patients with chronic kidney disease (CKD) [17]. Moreover, tubular creatinine secretion increases as the GFR decreases [8]. 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 CKD can affect creatinine secretion as well [9].

The serum protein cystatin C, an endogenous protein produced by all nucleated cells, is an alternative to creatinine for estimating GFR [18] and is preferred in children with decreased GFR [15, 19] and obese children [20]. There are also equations that use a combination of cystatin C and creatinine to determine eGFR [12, 18, 21]. A more complex formula, derived from the CKiD study, utilizes creatinine, cystatin C, blood urea nitrogen (BUN), height, and sex for estimating GFR [22].

For adult patients, the CKD-EPI creatinine equation [23] has generally replaced older equations such as the Cockcroft-Gault [24] and the Modification of Diet in Renal Disease (MDRD) equation [25]. There are also CKD-EPI equations that utilize cystatin C alone or cystatin C and serum creatinine [26].

In young adults, there are clearly limitations of the creatinine-derived equations. For an 18-year-old, the CKD-EPI creatinine equation provides a higher eGFR than the CKiD creatinine equation [27, 28]. Neither equation is accurate in young adults when compared to iohexol GFR [28]. The CKD-EPI equations using either cystatin C alone or cystatin C with creatinine are the best options, though an average of the CKD-EPI creatinine equation and the CKiD creatinine equation is also a reasonable option [28].

Predialysis Patient Monitoring and Preparation for Dialysis

Systematic patient monitoring is necessary in children with CKD 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, creation of a vascular access for hemodialysis, or performance of a preemptive kidney transplant. Table 9.1 outlines the necessary components for monitoring children with an eGFR < 30 ml/min/1.73 m^2.

In addition to medical monitoring, it is important that children and families are psychologically prepared for dialysis. This includes reviewing treatment options and exploring accommodations that will be needed at home and for the child's education.

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 kidney failure that cause significant morbidity and mortality. There is usually a dra-

Table 9.1 Evaluation schedule for children with stage IV–V chronic kidney disease

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, neurodevelopmental assessment in infants

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

matic or marked improvement with the 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 result in 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, especially if associated with weight loss.

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 whether there is a level of GFR that is an absolute indication for dialysis. There are recommendations that the presence of malnutrition is an indication for dialysis initiation. 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 prior to the institution of dialysis.

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 CKD [29, 30]. 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 [31]. Hyperkalemia usually does not become problematic until the GFR is less than 10–20 ml/min/1.73m^2, unless the potassium intake is excessive or excretion is reduced [31]. Hyperkalemia develops at a higher GFR in adults and children with hyporeninemic hypoaldosteronism, which may also cause a type IV renal tubular acidosis [31]. Similarly, other patients have a decreased tubular responsiveness to aldosterone, and this pseudohypoaldosteronism may cause hyperkalemia at higher levels of GFR [31]. 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 CKD 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 infant formula does not vary greatly, limiting the effectiveness of formula selection. It should be noted, however,

that soy-based and elemental formulas are especially high in potassium. Human milk has a 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, Renastart™, a formula with a very low potassium concentration, is used as a dietary supplement or is combined with another formula; it is not meant to be given as the sole source of nutrition [32].

Increasing potassium excretion can help ameliorate the hyperkalemia of CKD. Loop diuretics increase urinary potassium excretion. Discontinuation of medications that decrease urinary potassium excretion, such as ACE inhibitors, ARBs, nonsteroidal anti-inflammatory drugs, or potassium-sparing diuretics, can have a significant effect on the serum potassium level [33, 34]. Although not usually a significant mechanism of potassium excretion, stool potassium losses become more important as kidney function declines [35]. Constipation should be treated since it may decrease stool potassium losses [36]. Sodium polystyrene sulfonate (Kayexalate®), an exchange resin, binds potassium in the gastrointestinal tract, significantly increasing stool potassium losses. Pretreatment of formula with sodium polystyrene sulfonate is effective, but may cause constipation and problems with other electrolytes, including hypernatremia due to increased formula sodium content [37–39]. Newer oral potassium exchange resins include patiromer [40] and sodium zirconium cyclosilicate [41, 42]. There is some experience pre-treating formula with patiromer [43].

Because of the effectiveness of dietary and medical interventions, the 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 medications usually contributes to refractory hyperkalemia. Hemodialysis and peritoneal dialysis are quite effective at correcting hyperkalemia, although dietary restriction, and occasionally medical management, is usually still necessary.

Hyperphosphatemia

A decrease in filtered phosphate parallels the decrease in GFR characteristic of CKD. With mild to moderate kidney insufficiency, an increase in the fractional excretion of phosphate by the remaining nephrons initially compensates for the loss of functioning nephrons, permitting the serum phosphorus to remain normal [44]. As the GFR falls, compensation is inadequate, and hyperphosphatemia ensues, typically at CKD stage III [45, 46]. Hyperphosphatemia causes secondary hyperparathyroidism by suppressing 1,25-dihydroxyvitamin D production and calcium levels and through direct stimulation of PTH secretion [47]. Correction of hyperphosphatemia is essential for controlling secondary hyperparathyroidism. In addition, hyperphosphatemia may elevate the serum calcium-phosphorus product and contribute to vascular calcifications [48, 49]. In adult patients with CKD, serum phosphate levels predict mortality and progression of CKD [49–51], while fibroblast growth factor 23 (FGF23) levels, which increase in response to hyperphosphatemia, are a predictor of CKD progression in children [52].

The successful management of hyperphosphatemia in CKD depends on a reduction in phosphate intake by a combination of dietary phosphate restriction and the use of phosphate binders [53]. Early in kidney failure, before hyperphosphatemia develops, a reduction in phosphate intake helps to control secondary hyperparathyroidism [47]. As kidney function declines, dietary restriction alone, because of nutritional constraints and limitations of food palatability, is often inadequate to control hyperphosphatemia, necessitating the use of phosphate binders. Calcium carbonate and calcium acetate are effective phosphate binders in children with CKD, although excessive use may cause hypercalcemia and contribute to systemic calcifications [54]. Sevelamer, a calcium-free phosphate-binding agent, has been effectively utilized to control hyperphosphatemia in children

[55]. Additional calcium-free phosphate binders include lanthanum carbonate, sucroferric oxyhydroxide, and ferric citrate [56–59].

A majority of the available phosphate binders must be administered in large doses (several grams per day) to be effective; unfortunately, 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 the successful control of 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, non-adherence 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 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 [60–64]. In children, this may adversely affect growth [65]. Infants during the first 6 months of life, when growth is rapid, are particularly vulnerable to the negative effects of poor nutrition.

Studies in adult patients show an association between malnutrition when starting dialysis and decreased patient survival [62, 63, 66–75]. Nutritional parameters improve in adult patients after the initiation of dialysis [60, 63, 76–81]. 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 [78]. 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 [77, 79].

The improved survival with an increased dialysis dose, the mortality risk associated with malnutrition, and the improvement in nutritional status associated with dialysis are the basis for recommendations to initiate dialysis therapy when a patient has advanced CKD and malnutrition [82–84]. Yet, there are no prospective studies demonstrating that the early initiation of dialysis improves outcome. Aggressive nutritional supplementation, possibly using an enteral feeding gastrostomy tube, may reverse malnutrition in some children without the need for dialysis [85, 86].

There is no one ideal marker of malnutrition. Signs of poor nutrition in children with CKD may include inadequate weight gain, poor linear growth, and loss of muscle mass. If malnutrition is not improved via conservative interventions, then the child with advanced CKD should begin dialysis.

Growth Failure

Growth retardation is a common complication of CKD in children [87]. The causes of "uremic" growth failure include malnutrition (most markedly in infants), electrolyte and fluid losses (in children with hypo-/dysplastic kidney disorders), metabolic acidosis, osteodystrophy, 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 [88]. In children with stable predialytic CKD, recombinant growth hormone therapy is indicated. The efficacy of this therapy strongly depends on residual kidney function, mandating a timely start of treatment [89, 90]. Unresponsiveness to recombinant growth hor-

mone may be considered as an argument to start dialysis, although improved growth rates are not consistently observed after initiation of standard peritoneal or hemodialysis [91]. However, a subsequent study demonstrated that short daily hemodiafiltration improved responsiveness to growth hormone, leading to remarkable, complete catch-up growth [92]. 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 kidney function that is an absolute indication for initiating dialysis in children is uncertain. The adult literature is fraught with conflicting conclusions and opinions [93–95]. The debate is complicated by uncertainty regarding the best methodology for evaluating residual kidney function (see Section "Predialysis Patient Monitoring and Preparation for Dialysis"). The IDEAL study directly addressed this question in adults [96]. Patients were randomized to dialysis initiation at an eGFR of 10–15 ml/min/1.73 m^2 (early-start) or at an eGFR of 5–7 ml per minute (late-start). 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 [96].

In children, there are limited published studies. In a study of children in the United States Renal Data System (USRDS), higher eGFR at dialysis initiation was associated with a higher mortality, especially among patients who initiated hemodialysis [97]. In another study of children in the USRDS, mortality also increased as eGFR at dialysis initiation increased, especially among patients 6 years and older [98]. In a European study, there was no difference in mortality based on level of eGFR at dialysis initiation [99]. There are no randomized studies in children.

Estimated GFR at Dialysis Initiation

In adults, prior to the publication of the IDEAL trial, the eGFR at dialysis initiation was gradually increasing in many countries. However, this trend has either stabilized or reversed since the publication of the IDEAL trial [100, 101].

In a large cohort of European pediatric patients, the median eGFR at initiation of renal replacement therapy (RRT) was 10.4 ml/min/1.73 m^2, with the small percentage of patients who received a preemptive transplant having a significantly higher eGFR at the time of transplant (13.5 ml/min/1.73 m^2) [102]. Variables associated with a lower eGFR 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.

In a study of Canadian children, the median eGFR at dialysis initiation was 8.1 ml/min/1.73 m^2 [103]. Canadian children with a genetic cause of end-stage kidney disease (ESKD), living further from a treatment facility, and females were more likely to initiate dialysis at a higher eGFR. In a study of children in the USRDS, a higher eGFR at dialysis initiation was more common in whites, females, underweight or obese patients, and patients with glomerulonephritis as the underlying etiology of ESKD [97].

Consensus Statements Regarding Dialysis Initiation

The results of the IDEAL study have influenced guidelines on the timing of dialysis initiation; prior guidelines were more likely to reference a GFR threshold for initiating dialysis. The 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend dialysis initiation for specific indications, including symptoms or signs of kidney failure, refractory volume overload, hypertension or nutritional deterioration, and cognitive impairment [104]. Per these guidelines, this "often but not invariably" ensues at a GFR between 5 and 10 ml/min/1.73m^2.

The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommend similar clinical criteria to KDIGO for initiating dialysis [105]. The KDOQI guidelines do not provide a GFR criterion, citing the challenges of estimating GFR and the lack of evidence that decision-making based on GFR is beneficial. The European Best Practice Board (EBPB) guidelines on when to start dialysis were specifically updated in response to the IDEAL study [106]. These guidelines recommend consideration of initiation of dialysis when the GFR is <15 ml/min/1.73m^2 *and* there are specific indications, including signs or symptoms of uremia, uncontrolled hypertension or volume overload, or a deterioration in nutritional status. In addition, the EBPB guidelines emphasize that this will occur in the majority of patients at a GFR of 6–9 ml/min/1.73m^2 and that patients with rapid deterioration require close supervision [106].

The Canadian Society of Nephrology guidelines, updated in 2014, recommend an "intent to defer" strategy that involves careful monitoring of patients with a GFR < 15 ml/min/1.73m^2, with dialysis initiation when there are clinical indications. However, unlike other guidelines, it is recommended to initiate dialysis if the eGFR is 6 ml/min/1.73m^2 or less [107].

Arguments for Early ("Timely") Initiation

This was based on the observation that adults who start dialysis with a lower GFR have increased morbidity and mortality [108–110]. This may be secondary to the effects of malnutrition since decreased residual kidney function is associated with poor nutrition and poor nutrition when starting dialysis is associated with increased morbidity and mortality (see Section "Malnutrition"). Moreover, in the 1990s, many adult patients initiated dialysis at a lower GFR than was recommended [111–113]. 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 [100, 101]. This has been associated with subsequent observations suggesting that early initiation of dialysis may be harmful, with increasing mortality in patients who start early [114, 115]. However, this detrimental effect of early dialysis may be secondary to increased age and comorbidity in the patients who start early [116]. 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 eGFR due to poor nutritional status, a well-defined risk factor for morbidity and mortality. This would create additional bias suggesting that early initiation of dialysis is harmful. Similarly, a falsely low creatinine may also be present in malnourished children or children with comorbidities that may limit muscle mass (e.g., neurologic injury that prevents ambulation), and thus observational studies that analyze eGFR at dialysis initiation in children must be interpreted with caution.

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 [110]. These include lead-time bias, referral time bias, and patient selection [83]. 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 [118, 119]. Moreover, and as noted above, early initiation of dialysis may be associated with increased mortality [114, 115]. In adult and pediatric patients, late referral to a nephrologist is a predictor of poor outcomes [120–124]. Such patients are more likely to have a lower GFR at dialysis initiation, again tending to bias the out-

come against late initiation of dialysis. In addition, late referral patients are more likely to have a history of non-compliance with follow-up and more significant comorbid conditions [110].

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]. These issues are especially important in children given the need for a lifetime of ESKD 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 kidney function is associated with better outcomes in adults receiving dialysis [126, 127], and dialysis accelerates the loss of residual kidney function [128]. This is more significant with hemodialysis than continuous ambulatory peritoneal dialysis, in both adults and children [129–132]. The use of automated PD may [133, 134] or may not provoke a more rapid decline in residual kidney function than classical CAPD [132, 135]. Of particular relevance to children, it appears that short, high-turnover NIPD may exert similarly detrimental effects on residual kidney 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 the other factor.

Choice of Mode of Dialysis

Kidney transplantation is the optimal therapy for children with ESKD [136, 137]. However, transplantation is often not an immediate option because of the lack of a suitable donor. For some patients, psychosocial issues may also 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, though there is a trend for increased use of hemodialysis in the United States [138]. There is debate in the adult literature regarding the optimal form of therapy; however, there are no randomized studies that properly address this issue. Selection bias has made it difficult to perform comparative studies of morbidity and mortality between peritoneal dialysis and hemodialysis in pediatric patients [139].

Peritoneal dialysis may be especially advantageous during the first 2 years of therapy [140, 141]. This may be related to the improved preservation of residual kidney function with peritoneal dialysis [129, 130, 142]. 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 kidney 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 [144, 145]. Moreover, a high transporter state in children on peritoneal dialysis is associated with poor growth [146]. 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

Table 9.2 Contraindications to hemodialysis in children

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

Table 9.3 Contraindications to peritoneal dialysis in children

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

of living-related donors and their 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 [147–149]. 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 [150]. Problems include difficulties with vascular access, refractory anemia, inadequate urea removal, and the risk of hemodynamic instability [150]. 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 unless the patient has substantial residual kidney function.

The choice of dialysis modality is based on a number of considerations. There are relative and absolute contraindications for both modalities (see Tables 9.2 and 9.3). Psychosocial considerations are quite important given the family commitment needed to make peritoneal dialysis successful. Unless there are contraindications, peritoneal dialysis is the optimal modality for the majority of children, although both the family and the patient must be comfortable with the decision.

References

1. Pottel H. Measuring and estimating glomerular filtration rate in children. Pediatr Nephrol. 2017;32(2):249–63.
2. Schwartz GJ, Furth S, Cole SR, Warady B, Munoz A. Glomerular filtration rate via plasma iohexol disappearance: pilot study for chronic kidney disease in children. Kidney Int. 2006;69(11):2070–7.
3. Soveri I, Berg UB, Björk J, Elinder C-G, Grubb A, Mejare I, et al. Measuring GFR: a systematic review. Am J Kidney Dis. 2014;64(3):411–24.
4. Perrone RD, Steinman TI, Beck GJ, Skibinski CI, Royal HD, Lawlor M, et al. Utility of radioisotopic filtration markers in chronic renal insufficiency: simultaneous comparison of 125I-iothalamate, 169Yb-DTPA, 99mTc-DTPA, and inulin. The Modification of Diet in Renal Disease Study. Am J Kidney Dis. 1990;16(3):224–35.
5. Morton KA, Pisani DE, Whiting JH Jr, Cheung AK, Arias JM, Valdivia S. Determination of glomerular filtration rate using technetium-99m-DTPA with differing degrees of renal function. J Nucl Med Technol. 1997;25(2):110–4.
6. Delanaye P, Ebert N, Melsom T, Gaspari F, Mariat C, Cavalier E, et al. Iohexol plasma clearance for measuring glomerular filtration rate in clinical practice and research: a review. Part 1: how to measure glomerular filtration rate with iohexol? Clin Kidney J. 2016;9(5):682–99.
7. Li Y, Lee HB, Blaufox MD. Single-sample methods to measure GFR with technetium-99m-DTPA. J Nucl Med. 1997;38(8):1290–5.
8. Shemesh O, Golbetz H, Kriss JP, Myers BD. Limitations of creatinine as a filtration marker in glomerulopathic patients. Kidney Int. 1985;28(5):830–8.
9. Modification of Diet in Renal Disease Study Group. Effects of diet and antihypertensive therapy on creatinine clearance and serum creatinine concentration in the Modification of Diet in Renal Disease Study. J Am Soc Nephrol. 1996;7(4):556–66.
10. Lubowitz H, Slatopolsky E, Shankel S, Rieselbach RE, Bricker NS. Glomerular filtration rate. Determination in patients with chronic renal disease. JAMA. 1967;199(4):252–6.
11. van Olden RW, Krediet RT, Struijk DG, Arisz L. Measurement of residual renal function in patients treated with continuous ambulatory peritoneal dialysis. J Am Soc Nephrol. 1996;7(5):745–50.
12. Schwartz GJ, Work DF. Measurement and estimation of GFR in children and adolescents. Clin J Am Soc Nephrol. 2009;4(11):1832–43.
13. Schwartz GJ, Haycock GB, Edelmann CM Jr, Spitzer A. A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. Pediatrics. 1976;58(2):259–63.

14. De Souza VC, Rabilloud M, Cochat P, Selistre L, Hadj-Aissa A, Kassai B, et al. Schwartz formula: is one k-coefficient adequate for all children? PLoS One. 2012;7(12):e53439–e.
15. Björk J, Nyman U, Berg U, Delanaye P, Dubourg L, Goffin K, et al. Validation of standardized creatinine and cystatin C GFR estimating equations in a large multicentre European cohort of children. Pediatr Nephrol. 2019;34(6):1087–98.
16. Lewis J, Agodoa L, Cheek D, Greene T, Middleton J, O'Connor D, et al. Comparison of cross-sectional renal function measurements in African Americans with hypertensive nephrosclerosis and of primary formulas to estimate glomerular filtration rate. Am J Kidney Dis. 2001;38(4):744–53.
17. Mitch WE, Collier VU, Walser M. Creatinine metabolism in chronic renal failure. Clin Sci. 1980;58(4):327–35.
18. Andersen TB, Eskild-Jensen A, Frokiaer J, Brochner-Mortensen J. Measuring glomerular filtration rate in children; can cystatin C replace established methods? A review. Pediatr Nephrol. 2009;24(5):929–41.
19. Salvador CL, Tøndel C, Rowe AD, Bjerre A, Brun A, Brackman D, et al. Estimating glomerular filtration rate in children: evaluation of creatinine- and cystatin C-based equations. Pediatr Nephrol. 2019;34(2):301–11.
20. Correia-Costa L, Schaefer F, Afonso AC, Bustorff M, Guimaraes JT, Guerra A, et al. Normalization of glomerular filtration rate in obese children. Pediatr Nephrol. 2016;31(8):1321–8.
21. Zappitelli M, Parvex P, Joseph L, Paradis G, Grey V, Lau S, et al. Derivation and validation of cystatin C-based prediction equations for GFR in children. Am J Kidney Dis. 2006;48(2):221–30.
22. Schwartz GJ, Schneider MF, Maier PS, Moxey-Mims M, Dharnidharka VR, Warady BA, et al. Improved equations estimating GFR in children with chronic kidney disease using an immunonephelometric determination of cystatin C. Kidney Int. 2012;82(4):445–53.
23. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604–12.
24. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31–41.
25. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med. 1999;130(6):461–70.
26. Inker LA, Shaffi K, Levey AS. Estimating glomerular filtration rate using the chronic kidney disease-epidemiology collaboration creatinine equation: better risk predictions. Circ Heart Fail. 2012;5(3):303–6.
27. Selistre L, De Souza V, Cochat P, Antonello ICF, Hadj-Aissa A, Ranchin B, et al. GFR estimation in adolescents and young adults. J Am Soc Nephrol. 2012;23(6):989–96.
28. Ng DK, Schwartz GJ, Schneider MF, Furth SL, Warady BA. Combination of pediatric and adult formulas yield valid glomerular filtration rate estimates in young adults with a history of pediatric chronic kidney disease. Kidney Int. 2018;94(1):170–7.
29. Cowan ACJ, Gharib EG, Weir MA. Advances in the management of hyperkalemia in chronic kidney disease. Curr Opin Nephrol Hypertens. 2017;26(3):235–9.
30. Rodan AR. Potassium: friend or foe? Pediatr Nephrol. 2017;32(7):1109–21.
31. Palmer BF, Clegg DJ. Hyperkalemia across the continuum of kidney function. Clin J Am Soc Nephrol. 2018;13(1):155–7.
32. Keung LG. Renastart use in an infant on peritoneal dialysis. Adv Perit Dial. 2017;33:79–83.
33. Palmer BF. Renal complications associated with use of nonsteroidal anti-inflammatory agents. J Investig Med. 1995;43(6):516–33.
34. Bakris GL, Siomos M, Richardson D, Janssen I, Bolton WK, Hebert L, et al. ACE inhibition or angiotensin receptor blockade: impact on potassium in renal failure. VAL-K Study Group. Kidney Int. 2000;58(5):2084–92.
35. Hayes CP Jr, McLeod ME, Robinson RR. An extravenal mechanism for the maintenance of potassium balance in severe chronic renal failure. Trans Assoc Am Phys. 1967;80:207–16.
36. Allon M. Treatment and prevention of hyperkalemia in end-stage renal disease. Kidney Int. 1993;43(6):1197–209.
37. Shahar-Nissan K, Peled O, Krause I. The ice cream challenge: a favourable extemporaneous Kayexalate formulation improves compliance in paediatric patients. Br J Clin Pharmacol. 2019;85(10):2450–2.
38. Thompson K, Flynn J, Okamura D, Zhou L. Pretreatment of formula or expressed breast milk with sodium polystyrene sulfonate (Kayexalate(®)) as a treatment for hyperkalemia in infants with acute or chronic renal insufficiency. J Ren Nutr. 2013;23(5):333–9.
39. Le Palma K, Pavlick ER, Copelovitch L. Pretreatment of enteral nutrition with sodium polystyrene sulfonate: effective, but beware the high prevalence of electrolyte derangements in clinical practice. Clin Kidney J. 2018;11(2):166–71.
40. Bakris GL, Pitt B, Weir MR, Freeman MW, Mayo MR, Garza D, et al. Effect of Patiromer on serum potassium level in patients with hyperkalemia and diabetic kidney disease: the AMETHYST-DN randomized clinical trial. JAMA. 2015;314(2):151–61.
41. Kosiborod M, Peacock WF, Packham DK. Sodium zirconium cyclosilicate for urgent therapy of severe hyperkalemia. N Engl J Med. 2015;372(16):1577–8.

42. Packham DK, Kosiborod M. Pharmacodynamics and pharmacokinetics of sodium zirconium cyclosilicate [ZS-9] in the treatment of hyperkalemia. Expert Opin Drug Metab Toxicol. 2016;12(5):567–73.
43. Paloian NJ, Bowman B, Bartosh SM. Treatment of infant formula with patiromer dose dependently decreases potassium concentration. Pediatr Nephrol. 2019;34(8):1395–401.
44. Portale AA, Booth BE, Halloran BP, Morris RC Jr. Effect of dietary phosphorus on circulating concentrations of 1,25-dihydroxyvitamin D and immunoreactive parathyroid hormone in children with moderate renal insufficiency. J Clin Invest. 1984;73(6):1580–9.
45. Levin A, Bakris GL, Molitch M, Smulders M, Tian J, Williams LA, et al. Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: results of the study to evaluate early kidney disease. Kidney Int. 2007;71(1):31–8.
46. Portale AA, Wolf M, Jüppner H, Messinger S, Kumar J, Wesseling-Perry K, et al. Disordered FGF23 and mineral metabolism in children with CKD. Clin J Am Soc Nephrol. 2014;9(2):344–53.
47. Wesseling-Perry K, Salusky IB. Chronic kidney disease: mineral and bone disorder in children. Semin Nephrol. 2013;33(2):169–79.
48. Adeney KL, Siscovick DS, Ix JH, Seliger SL, Shlipak MG, Jenny NS, et al. Association of serum phosphate with vascular and valvular calcification in moderate CKD. J Am Soc Nephrol. 2009;20(2):381–7.
49. Lezaic V, Tirmenstajn-Jankovic B, Bukvic D, Vujisic B, Perovic M, Novakovic N, et al. Efficacy of hyperphosphatemia control in the progression of chronic renal failure and the prevalence of cardiovascular calcification. Clin Nephrol. 2009;71(1):21–9.
50. Kestenbaum B, Sampson JN, Rudser KD, Patterson DJ, Seliger SL, Young B, et al. Serum phosphate levels and mortality risk among people with chronic kidney disease. J Am Soc Nephrol. 2005;16(2):520–8.
51. Voormolen N, Noordzij M, Grootendorst DC, Beetz I, Sijpkens YW, van Manen JG, et al. High plasma phosphate as a risk factor for decline in renal function and mortality in pre-dialysis patients. Nephrol Dial Transplant. 2007;22(10):2909–16.
52. Portale AA, Wolf MS, Messinger S, Perwad F, Jüppner H, Warady BA, et al. Fibroblast growth factor 23 and risk of CKD progression in children. Clin J Am Soc Nephrol. 2016;11(11):1989–98.
53. Rees L, Shroff RC. Phosphate binders in CKD: chalking out the differences. Pediatr Nephrol. 2010;25(3):385–94.
54. Goodman WG, Goldin J, Kuizon BD, Yoon C, Gales B, Sider D, et al. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. N Engl J Med. 2000;342(20):1478–83.
55. Hahn D, Hodson EM, Craig JC. Interventions for metabolic bone disease in children with chronic kidney disease. Cochrane Database Syst Rev. 2015(11):CD008327-CD.
56. Hutchison AJ, Wilson RJ, Garafola S, Copley JB. Lanthanum carbonate: safety data after 10 years. Nephrology. 2016;21(12):987–94.
57. Floege J, Covic AC, Ketteler M, Rastogi A, Chong EM, Gaillard S, et al. A phase III study of the efficacy and safety of a novel iron-based phosphate binder in dialysis patients. Kidney Int. 2014;86(3):638–47.
58. Lewis JB, Sika M, Koury MJ, Chuang P, Schulman G, Smith MT, et al. Ferric citrate controls phosphorus and delivers iron in patients on dialysis. J Am Soc Nephrol. 2015;26(2):493–503.
59. Klings ES, Machado RF, Barst RJ, Morris CR, Mubarak KK, Gordeuk VR, et al. An official American Thoracic Society clinical practice guideline: diagnosis, risk stratification, and management of pulmonary hypertension of sickle cell disease. Am J Respir Crit Care Med. 2014;189(6):727–40.
60. Pollock CA, Ibels LS, Zhu FY, Warnant M, Caterson RJ, Waugh DA, et al. Protein intake in renal disease. J Am Soc Nephrol. 1997;8(5):777–83.
61. Kopple JD, Greene T, Chumlea WC, Hollinger D, Maroni BJ, Merrill D, et al. Relationship between nutritional status and the glomerular filtration rate: results from the MDRD study. Kidney Int. 2000;57(4):1688–703.
62. Ikizler TA, Greene JH, Wingard RL, Parker RA, Hakim RM. Spontaneous dietary protein intake during progression of chronic renal failure. J Am Soc Nephrol. 1995;6(5):1386–91.
63. McCusker FX, Teehan BP, Thorpe KE, Keshaviah PR, Churchill DN. How much peritoneal dialysis is required for the maintenance of a good nutritional state? Canada-USA (CANUSA) Peritoneal Dialysis Study Group. Kidney Int. 1996;56:S56–61.
64. Norman LJ, Coleman JE, Macdonald IA, Tomsett AM, Watson AR. Nutrition and growth in relation to severity of renal disease in children. Pediatr Nephrol. 2000;15(3–4):259–65.
65. Sedman A, Friedman A, Boineau F, Strife CF, Fine R. Nutritional management of the child with mild to moderate chronic renal failure. J Pediatr. 1996;129(2):s13–8.
66. U.S. Renal Data Systems (USRDS). Comorbid conditions and correlations with mortality risk among 3,399 incident hemodialysis patients. Am J Kidney Dis. 1992;20(5 Suppl 2):32–8.
67. Churchill DN, Taylor DW, Cook RJ, LaPlante P, Barre P, Cartier P, et al. Canadian hemodialysis morbidity study. Am J Kidney Dis. 1992;19(3):214–34.
68. Lowrie EG, Lew NL. Death risk in hemodialysis patients: the predictive value of commonly measured variables and an evaluation of death rate differences between facilities. Am J Kidney Dis. 1990;15(5):458–82.
69. Bergstrom J. Nutrition and mortality in hemodialysis. J Am Soc Nephrol. 1995;6(5):1329–41.
70. Iseki K, Uehara H, Nishime K, Tokuyama K, Yoshihara K, Kinjo K, et al. Impact of the initial lev-

els of laboratory variables on survival in chronic dialysis patients. Am J Kidney Dis. 1996;28(4):541–8.
71. Avram MM, Mittman N, Bonomini L, Chattopadhyay J, Fein P. Markers for survival in dialysis: a seven-year prospective study. Am J Kidney Dis. 1995;26(1):209–19.
72. Barrett BJ, Parfrey PS, Morgan J, Barre P, Fine A, Goldstein MB, et al. Prediction of early death in end-stage renal disease patients starting dialysis. Am J Kidney Dis. 1997;29(2):214–22.
73. Kopple JD, Zhu X, Lew NL, Lowrie EG. Body weight-for-height relationships predict mortality in maintenance hemodialysis patients. Kidney Int. 1999;56(3):1136–48.
74. Leavey SF, Strawderman RL, Jones CA, Port FK, Held PJ. Simple nutritional indicators as independent predictors of mortality in hemodialysis patients. Am J Kidney Dis. 1998;31(6):997–1006.
75. Canada-USA (CANUSA) Peritoneal Dialysis Study Group. Adequacy of dialysis and nutrition in continuous peritoneal dialysis: association with clinical outcomes. J Am Soc Nephrol. 1996;7(2):198–207.
76. Blake PG, Flowerdew G, Blake RM, Oreopoulos DG. Serum albumin in patients on continuous ambulatory peritoneal dialysis--predictors and correlations with outcomes. J Am Soc Nephrol. 1993;3(8):1501–7.
77. Pupim LB, Kent P, Caglar K, Shyr Y, Hakim RM, Ikizler TA. Improvement in nutritional parameters after initiation of chronic hemodialysis. Am J Kidney Dis. 2002;40(1):143–51.
78. Ishimura E, Okuno S, Kim M, Yamamoto T, Izumotani T, Otoshi T, et al. Increasing body fat mass in the first year of hemodialysis. J Am Soc Nephrol. 2001;12(9):1921–6.
79. Goldwasser P, Kaldas AI, Barth RH. Rise in serum albumin and creatinine in the first half year on hemodialysis. Kidney Int. 1999;56(6):2260–8.
80. Parker TF 3rd, Wingard RL, Husni L, Ikizler TA, Parker RA, Hakim RM. Effect of the membrane biocompatibility on nutritional parameters in chronic hemodialysis patients. Kidney Int. 1996;49(2):551–6.
81. Mehrotra R, Berman N, Alistwani A, Kopple JD. Improvement of nutritional status after initiation of maintenance hemodialysis. Am J Kidney Dis. 2002;40(1):133–42.
82. National Kidney Foundation. KDOQI clinical practice guidelines for peritoneal dialysis adequacy: 2006 update. Am J Kidney Dis. 2006;48(suppl 2):S91–S175.
83. Churchill DN, Blake PG, Jindal KK, Toffelmire EB, Goldstein MB. Clinical practice guidelines for initiation of dialysis. Canadian Society of Nephrology. J Am Soc Nephrol. 1999;10(Suppl 13):S289–91.
84. Kelly J, Stanley M, Harris D. The CARI guidelines. Acceptance into dialysis guidelines. Nephrology. 2005;10(Suppl 4):S46–60.
85. Parekh RS, Flynn JT, Smoyer WE, Milne JL, Kershaw DB, Bunchman TE, et al. Improved growth in young children with severe chronic renal insufficiency who use specified nutritional therapy. J Am Soc Nephrol. 2001;12(11):2418–26.
86. Rees L, Brandt ML. Tube feeding in children with chronic kidney disease: technical and practical issues. Pediatr Nephrol. 2010;25(4):699–704.
87. Greenbaum LA, Warady BA, Furth SL. Current advances in chronic kidney disease in children: growth, cardiovascular, and neurocognitive risk factors. Semin Nephrol. 2009;29(4):425–34.
88. Feneberg R, Bürkel E, Sahm K, Weck K, Mehls O, Schaefer F. Long-term effects of tube feeding on growth and body composition in uremic infants. J Am Soc Nephrol. 2001;12:A2200.
89. Koch VH, Lippe BM, Nelson PA, Boechat MI, Sherman BM, Fine RN. Accelerated growth after recombinant human growth hormone treatment of children with chronic renal failure. J Pediatr. 1989;115(3):365–71.
90. Schaefer F, Haffner D, Wuhl E, Mehls O. Long-term experience with growth hormone treatment in children with chronic renal failure. Perit Dial Int. 1999;19(Suppl 2):S467–72.
91. Neu AM, Ho PL, McDonald RA, Warady BA. Chronic dialysis in children and adolescents. The 2001 NAPRTCS annual report. Pediatr Nephrol. 2002;17(8):656–63.
92. Fischbach M, Terzic J, Menouer S, Dheu C, Seuge L, Zalosczic A. Daily on line haemodiafiltration promotes catch-up growth in children on chronic dialysis. Nephrol Dial Transplant. 2010;25(3):867–73.
93. Janmaat CJ, van Diepen M, Krediet RT, Hemmelder MH, Dekker FW. Effect of glomerular filtration rate at dialysis initiation on survival in patients with advanced chronic kidney disease: what is the effect of lead-time bias? Clin Epidemiol. 2017;9:217–30.
94. Crews DC, Scialla JJ, Boulware LE, Navaneethan SD, Nally JV Jr, Liu X, et al. Comparative effectiveness of early versus conventional timing of dialysis initiation in advanced CKD. Am J Kidney Dis. 2014;63(5):806–15.
95. Rosansky SJ, Eggers P, Jackson K, Glassock R, Clark WF. Early start of hemodialysis may be harmful. Arch Intern Med. 2011;171(5):396–403.
96. Cooper BA, Branley P, Bulfone L, Collins JF, Craig JC, Fraenkel MB, et al. A randomized, controlled trial of early versus late initiation of dialysis. N Engl J Med. 2010;363(7):609–19.
97. Winnicki E, Johansen KL, Cabana MD, Warady BA, McCulloch CE, Grimes B, et al. Higher eGFR at dialysis initiation is not associated with a survival benefit in children. J Am Soc Nephrol. 2019;30(8):1505–13.
98. Okuda Y, Soohoo M, Tang Y, Obi Y, Laster M, Rhee CM, et al. Estimated GFR at Dialysis initiation and mortality in children and adolescents. Am J Kidney Dis. 2019;73(6):797–805.
99. Preka E, Bonthuis M, Harambat J, Jager KJ, Groothoff JW, Baiko S, et al. Association between timing of dialysis initiation and clinical outcomes

in the paediatric population: an ESPN/ERA-EDTA registry study. Nephrol Dial Transplant. 2019;34(11):1932–40.
100. Li Y, Jin Y, Kapke A, Pearson J, Saran R, Port FK, et al. Explaining trends and variation in timing of dialysis initiation in the United States. Medicine. 2017;96(20):e6911–e.
101. Ferguson TW, Garg AX, Sood MM, Rigatto C, Chau E, Komenda P, et al. Association between the publication of the initiating dialysis early and late trial and the timing of dialysis initiation in Canada. JAMA Intern Med. 2019;179(7):934–41.
102. van Stralen KJ, Tizard EJ, Jager KJ, Schaefer F, Vondrak K, Groothoff JW, et al. Determinants of eGFR at start of renal replacement therapy in paediatric patients. Nephrol Dial Transplant. 2010;25(10):3325–32.
103. Dart AB, Zappitelli M, Sood MM, Alexander RT, Arora S, Erickson RL, et al. Variation in estimated glomerular filtration rate at dialysis initiation in children. Pediatr Nephrol. 2017;32(2):331–40.
104. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013;3:1–150.
105. National Kidney Foundation KDOQI Clinical Practice Guideline for Hemodialysis Adequacy. 2015 update. Am J Kidney Dis. 2015;66(5):884–930.
106. Tattersall J, Dekker F, Heimburger O, Jager KJ, Lameire N, Lindley E, et al. When to start dialysis: updated guidance following publication of the Initiating Dialysis Early and Late (IDEAL) study. Nephrol Dial Transplant. 2011;26(7):2082–6.
107. Nesrallah GE, Mustafa RA, Clark WF, Bass A, Barnieh L, Hemmelgarn BR, et al. Canadian Society of Nephrology 2014 clinical practice guideline for timing the initiation of chronic dialysis. CMAJ. 2014;186(2):112–7.
108. Bonomini V, Feletti C, Scolari MP, Stefoni S. Benefits of early initiation of dialysis. Kidney Int. 1985;17(9):S57–9.
109. Tattersall J, Greenwood R, Farrington K. Urea kinetics and when to commence dialysis. Am J Nephrol. 1995;15(4):283–9.
110. Churchill DN. An evidence-based approach to earlier initiation of dialysis. Am J Kidney Dis. 1997;30(6):899–906.
111. Van Biesen W, Wiedemann M, Lameire N. End-stage renal disease treatment: a European perspective. J Am Soc Nephrol. 1998;9(12 Suppl):S55–62.
112. Mehrotra R, Lee J, Elivera H, Ahmed Z. Trends in initiation of dialysis in an urban dialysis clinic in the United States: a long way from dialysis outcomes quality initiative guidelines. Adv Perit Dial. 1999;15:138–43.
113. Obrador GT, Arora P, Kausz AT, Ruthazer R, Pereira BJ, Levey AS. Level of renal function at the initiation of dialysis in the U.S. end-stage renal disease population. Kidney Int. 1999;56(6):2227–35.
114. Beddhu S, Samore MH, Roberts MS, Stoddard GJ, Ramkumar N, Pappas LM, et al. Impact of timing of initiation of dialysis on mortality. J Am Soc Nephrol. 2003;14(9):2305–12.
115. Kazmi WH, Gilbertson DT, Obrador GT, Guo H, Pereira BJ, Collins AJ, et al. Effect of comorbidity on the increased mortality associated with early initiation of dialysis. Am J Kidney Dis. 2005;46(5):887–96.
116. Lassalle M, Labeeuw M, Frimat L, Villar E, Joyeux V, Couchoud C, et al. Age and comorbidity may explain the paradoxical association of an early dialysis start with poor survival. Kidney Int. 2010;77(8):700–7.
117. Beddhu S, Pappas LM, Ramkumar N, Samore M. Effects of body size and body composition on survival in hemodialysis patients. J Am Soc Nephrol. 2003;14(9):2366–72.
118. Korevaar JC, Jansen MA, Dekker FW, Jager KJ, Boeschoten EW, Krediet RT, et al. When to initiate dialysis: effect of proposed US guidelines on survival. Lancet. 2001;358(9287):1046–50.
119. Traynor JP, Simpson K, Geddes CC, Deighan CJ, Fox JG. Early initiation of dialysis fails to prolong survival in patients with end-stage renal failure. J Am Soc Nephrol. 2002;13:2125–32.
120. Chow KM, Szeto CC, Law MC, Kwan BC, Leung CB, Li PK. Impact of early nephrology referral on mortality and hospitalization in peritoneal dialysis patients. Perit Dial Int. 2008;28(4):371–6.
121. Hasegawa T, Bragg-Gresham JL, Yamazaki S, Fukuhara S, Akizawa T, Kleophas W, et al. Greater first-year survival on hemodialysis in facilities in which patients are provided earlier and more frequent pre-nephrology visits. Clin J Am Soc Nephrol. 2009;4(3):595–602.
122. McClellan WM, Wasse H, McClellan AC, Kipp A, Waller LA, Rocco MV. Treatment center and geographic variability in pre-ESRD care associate with increased mortality. J Am Soc Nephrol. 2009;20(5):1078–85.
123. Lee BJ, Forbes K. The role of specialists in managing the health of populations with chronic illness: the example of chronic kidney disease. BMJ. 2009;339:b2395.
124. Jander A, Nowicki M, Tkaczyk M, Roszkowska-Blaim M, Jarmoliński T, Marczak E, et al. Does a late referral to a nephrologist constitute a problem in children starting renal replacement therapy in Poland?--a nationwide study. Nephrol Dial Transplant. 2006;21(4):957–61.
125. Andreoli SP, Langefeld CD, Stadler S, Smith P, Sears A, West K. Risks of peritoneal membrane failure in children undergoing long-term peritoneal dialysis. Pediatr Nephrol. 1993;7(5):543–7.
126. Termorshuizen F, Dekker FW, van Manen JG, Korevaar JC, Boeschoten EW, Krediet RT. Relative contribution of residual renal function and different measures of adequacy to survival in hemodialysis patients: an analysis of the Netherlands Cooperative

Study on the Adequacy of Dialysis (NECOSAD)-2. J Am Soc Nephrol. 2004;15(4):1061–70.
127. Paniagua R, Amato D, Vonesh E, Correa-Rotter R, Ramos A, Moran J, et al. Effects of increased peritoneal clearances on mortality rates in peritoneal dialysis: ADEMEX, a prospective, randomized, controlled trial. J Am Soc Nephrol. 2002;13(5):1307–20.
128. Rottembourg J. Residual renal function and recovery of renal function in patients treated by CAPD. Kidney Int. 1993;40:S106–10.
129. Lang SM, Bergner A, Topfer M, Schiffl H. Preservation of residual renal function in dialysis patients: effects of dialysis-technique-related factors. Perit Dial Int. 2001;21(1):52–7.
130. Schulman G. The role of hemodialysis and peritoneal dialysis for the early initiation of dialysis. Blood Purif. 2001;19(2):175–8.
131. Feber J, Scharer K, Schaefer F, Mikova M, Janda J. Residual renal function in children on haemodialysis and peritoneal dialysis therapy. Pediatr Nephrol. 1994;8(5):579–83.
132. Fischbach M, Terzic J, Menouer S, Soulami K, Dangelser C, Helmstetter A, et al. Effects of automated peritoneal dialysis on residual daily urinary volume in children. Adv Perit Dial. 2001;17:269–73.
133. Hufnagel G, Michel C, Queffeulou G, Skhiri H, Damieri H, Mignon F. The influence of automated peritoneal dialysis on the decrease in residual renal function. Nephrol Dial Transplant. 1999;14(5):1224–8.
134. Hiroshige K, Yuu K, Soejima M, Takasugi M, Kuroiwa A. Rapid decline of residual renal function in patients on automated peritoneal dialysis. Perit Dial Int. 1996;16(3):307–15.
135. de Fijter CW, ter Wee PM, Donker AJ. The influence of automated peritoneal dialysis on the decrease in residual renal function. Nephrol Dial Transplant. 2000;15(7):1094–6.
136. McDonald SP, Craig JC. Australian, New Zealand Paediatric Nephrology A. Long-term survival of children with end-stage renal disease. N Engl J Med. 2004;350(26):2654–62.
137. Chesnaye NC, van Stralen KJ, Bonthuis M, Harambat J, Groothoff JW, Jager KJ. Survival in children requiring chronic renal replacement therapy. Pediatr Nephrol. 2018;33(4):585–94.
138. Weaver DJ Jr, Somers MJG, Martz K, Mitsnefes MM. Clinical outcomes and survival in pediatric patients initiating chronic dialysis: a report of the NAPRTCS registry. Pediatr Nephrol. 2017;32(12):2319–30.
139. Litwin M, Grenda R, Prokurat S, Abuauba M, Latoszynska J, Jobs K, et al. Patient survival and causes of death on hemodialysis and peritoneal dialysis--single-center study. Pediatr Nephrol. 2001;16(12):996–1001.
140. Fenton SS, Schaubel DE, Desmeules M, Morrison HI, Mao Y, Copleston P, et al. Hemodialysis versus peritoneal dialysis: a comparison of adjusted mortality rates. Am J Kidney Dis. 1997;30(3):334–42.
141. Collins AJ, Hao W, Xia H, Ebben JP, Everson SE, Constantini EG, et al. Mortality risks of peritoneal dialysis and hemodialysis. Am J Kidney Dis. 1999;34(6):1065–74.
142. Coles GA, Williams JD. What is the place of peritoneal dialysis in the integrated treatment of renal failure? Kidney Int. 1998;54(6):2234–40.
143. Alloatti S, Manes M, Paternoster G, Gaiter AM, Molino A, Rosati C. Peritoneal dialysis compared with hemodialysis in the treatment of end-stage renal disease. J Nephrol. 2000;13(5):331–42.
144. Davies SJ, Phillips L, Griffiths AM, Russell LH, Naish PF, Russell GI. What really happens to people on long-term peritoneal dialysis? Kidney Int. 1998;54(6):2207–17.
145. Wang T, Heimburger O, Waniewski J, Bergstrom J, Lindholm B. Increased peritoneal permeability is associated with decreased fluid and small-solute removal and higher mortality in CAPD patients. Nephrol Dial Transplant. 1998;13(5):1242–9.
146. Schaefer F, Klaus G, Mehls O. Peritoneal transport properties and dialysis dose affect growth and nutritional status in children on chronic peritoneal dialysis. Mid-European Pediatric Peritoneal Dialysis Study Group. J Am Soc Nephrol. 1999;10(8):1786–92.
147. Maiorca R, Vonesh E, Cancarini GC, Cantaluppi A, Manili L, Brunori G, et al. A six-year comparison of patient and technique survivals in CAPD and HD. Kidney Int. 1988;34(4):518–24.
148. Vonesh EF, Moran J. Mortality in end-stage renal disease: a reassessment of differences between patients treated with hemodialysis and peritoneal dialysis. J Am Soc Nephrol. 1999;10(2):354–65.
149. Tanna MM, Vonesh EF, Korbet SM. Patient survival among incident peritoneal dialysis and hemodialysis patients in an urban setting. Am J Kidney Dis. 2000;36(6):1175–82.
150. Al-Hermi BE, Al-Saran K, Secker D, Geary DF. Hemodialysis for end-stage renal disease in children weighing less than 10 kg. Pediatr Nephrol. 1999;13(5):401–3.