Special Issues Related to Pediatric Patients on Dialysis

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Introduction / Overview

The many medical problems that affect patients with end-stage renal disease (ESRD) who require life-maintaining dialytic therapies may have a somewhat different and often very significant impact on the lives of infants, children, and adolescents (compared with adults) with renal failure. Therapy for renal failure in infants and children is often quite challenging considering the infant or child's small size together with the increased metabolic demands of the growing and developing human. The relative physiologic homeostasis that is needed to support the physical and emotional growth and maturation of a child, combined with the complex interpersonal and multidisciplinary interactions required in caring for these patients, suggests the need for a coordinated team of individuals with interest and expertise in the management of children with ESRD. This chapter will address the causes of ESRD in children, the indications for considering dialysis therapies, some of the modifications needed in the institution of chronic peritoneal dialysis (PD) and hemodialysis (HD) in infants and children, including choices of dialysis modalities, differences in dialysis prescriptions, and other issues of medical significance in these children including nutritional considerations, statural growth, and osteodystrophy.

Incidence and Etiologies of ESRD in Children

The spectrum of causes of ESRD in infants and children is somewhat different compared with the causes of ESRD in adults. Recently data regarding the causes of ESRD was reported by The North American Pediatric Renal Transplant Cooperative Study (NAPRTCS), a research effort organized and initiated in 1987 originally designed to capture information about practices and trends in immunosuppressive therapy with an ultimate goal of improving the care of pediatric renal transplant recipients [2]. More recently, this cooperative study was expanded to included data on young patients on PD and HD [5] and those with chronic renal failure (CRF) [78]. In the most recent report from this cooperative study [78], when evaluating the causes of ESRD leading to renal transplantation, 3 of the 4 leading causes of CRF were congenital urinary tract disorders (including obstructive uropathy, aplastic/hypoplastic/dysplastic kidneys, and reflux nephropathy). Children with vesicoureteral reflux and some forms of congenital obstructive uropathy may have conditions that are potentially treatable if diagnosed early in life, or diagnosed on prenatal ultrasound. The leading causes of ESRD in the adult age groups, diabetes and hypertension [28], are quite unusual causes of ESRD in

Table 1. Causes of ESRD in Children Resulting in Renal Transplantation

Disease/Condition	Percent
Obstructive uropathy	16.5
Aplastic/hypoplastic/dysplastic kidneys	16.4
Focal segmental glomerulosclerosis	11.6
Reflux nephropathy	5.7
Systemic immunologic disease	4.7
Chronic glomerulonephritis	4.4
Syndrome of agenesis of the abdominal musculature	3.0
Congenital nephrotic syndrome	2.8
Hemolytic uremic syndrome	2.7
Polycystic kidney disease	2.7
Medullary cystic disease/juvenile nephronopthisis	2.6
Cystinosis	2.5
Pyelonephritis/interstitial nephritis	2.3
Membranoproliferative glomerulonephritis type I	2.3
Familial nephritis	2.3
Renal infarct	2.0
Idiopathic crescentic glomerulonephritis	1.8
Membranoproliferative glomerulonephritis type I	1.0
Oxalosis	0.8
Membranous nephropathy	0.6
Wilms tumor	0.6
Drash syndrome	0.5
Sickle cell nephropathy	0.1
Diabetic nephropathy	0.1
Unknown	4.4

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children. Table 1 lists causes of ESRD leading to renal transplantation in children.

Pediatric patients < 20 years of age with treated ESRD (from 1988 – 1992) numbered 4,352 patients, compared with 234,296 total number patients with treated ESRD in the United States from 1988 to 1992 [28]. Table 2 compares the incidence and causes of ESRD in children and adults. It can be noted from this table that while the percentage of adults patients having ESRD from congenital causes is markedly lower than reported in children (0.7 percent in adults compared with 18.5 percent in children), the ages at which these congenital disease cause ESRD in adults are markedly lower than the mean age at onset of ESRD (from all causes) in adults.

Indications for Initiation of Dialysis

Over the past decade, and certainly over the past 5 years, pediatric nephrologists have been judging the need for the initiation of chronic dialysis therapies based on the overall clinical status of the patient, with less reliance

Table 2. Incidence of Treated ESRD in Children and Adults (1988-1992) (Data for adults in parenthesis)

Primary Disease	Total Incidence Count	Percentage of Total	Median Age
All pediatric ESRD	4352 (234,296)	100 (100)	15 (62)
Diabetes	52 (80,834)	1.4 (36.2)	18 (61)
Hypertension	210 (67,239)	5.5 (30.1)	17 (68)
Glomerulonephritis	1387 (28,739)	36 (12.9)	16 (54)
Goodpasture syndrome	20 (719)	0.5 (0.3)	18 (65)
Focal glomerulosclerosis	30 (3,512)	9.1 (1.6)	15 (40)
Membranous nephropathy	23 (1,083)	0.6 (0.5)	15 (56)
Membranoproliferative GN	128 (881)	3.3 (0.4)	15(42)
Other glomerulonephritis	866 (22,544)	22.5 (10.1)	16 (56)
Cystic kidney disease	170 (6,978)	4.4 (3.1)	11 (54)
Interstitial nephritis	169 (7,011)	4.4 (3.1)	16 (63)
Analgesic nephropathy	32 (1,884)	0.8 (0.8)	14 (64)
All other interstitial nephritis	137 (5,127)	3.6 (2.3)	16 (63)
Obstructive uropathy	304 (4,792)	7.9 (2.1)	12 (68)
Collagen vascular diseases	362 (4,982)	9.4 (2.2)	16 (41)
Systemic lupus erythematosus	242 (3,147)	6.3 (1.4)	16 (35)
Scleroderma	NR (546)	NR (0.2)	NR (58)
Wegner's granulomatosis	14 (557)	0.4 (0.2)	16 (63)
Hemolytic uremic syndrome/thrombotic thromboytopenic purpura	67 (483)	1.7 (0.2)	8 (49)
Polyarteritis	NR (127)	NR (0.1)	NR (58)
Henoch-Schonlein purpura	33 (93)	0.9 (0.0)	15 (27)
Rheumatoid arthritis	NR (29)	NR (0.0)	NR (64)
Malignancies	12 (2,962)	0.3 (1.3)	4 (68)
Metabolic diseases	51 (1,143)	1.3 (0.5)	10 (62)
Cystinosis	38 (51)	1 (0.0)	11 (12)
Oxalate nephropathy	13 (89)	0.3 (0.0)	10 (57)
Congenital/other hereditary diseases	710 (1,611)	18.5 (0.7)	11 (22)
Congenital obstructive uropathy	156 (409)	4.1 (0.2)	12 (27)
Renal dysgenesis, agenesis, dysplasia	173 (382)	4.5 (0.2)	9 (22)
Alport syndrome	381(820)	9.9 (0.4)	11 (21)

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on laboratory values representing the degree of renal functional impairment (i.e. blood urea nitrogen (BUN) or serum creatinine levels). In general, with the recent availability of medications to promote the correction of anemia (recombinant human erythopoietin [rHu-EPO]), to ameliorate the significant growth retardation affecting most young children with ESRD (recombinant human growth hormone [rhGH]), and to provide activated vitamin D (calcitriol), the initiation of chronic dialysis often occurs later in children, with levels of serum creatinine somewhat higher than previously encountered at the initiation

of dialysis. As such, there is no particular laboratory value that should be used to justify the initiation of chronic dialytic therapies. Certainly if the child has significant hyperkalemia unresponsive to dietary and pharmacologic therapies, severe acidosis which is unable to be controlled with administration of alkali, uremic pericarditis, or uremic encephalopathy, the need for dialysis becomes clear. In addition, decreased school performance, cognitive development, and psychosocial/behavioral impairment may also prompt the initiation of dialysis and perhaps other therapeutic interventions in children with chronic renal failure [19]. Once it becomes clear to the pediatric nephrologist that dialysis will soon be needed, a decision regarding the method of dialytic therapy will need to be made, and arrangements made for creating either vascular or peritoneal access (or both).

Choice of Dialysis Modality

The decision regarding the methodology of dialysis depends on a number of factors related both to the patient and to the dialysis center's experience and preference. In North America, approximately 66% of persons < 21 years of age with ESRD requiring dialysis were treated with PD, while 34% were treated with HD, in data collected from 1987 through 1992 [4]. However, the relative contribution of PD and HD in the treatment of children with ESRD requiring dialysis varies worldwide on a country to country basis. The European Dialysis and Transplantation Association reported recently that 29% of newly dialyzed children were treated with PD, while 50% of those < 2 years of age were placed on PD [27]. The use of PD as maintenance renal replacement therapy has continued to expand over the past 15 years, and reports suggest that the majority of children (50 – 75%) can be successfully treated with chronic PD for at least several years while awaiting renal transplantation [3].

Despite the recent increase in the use of PD to treat ESRD in children, HD continues to be a viable option in adolescents and older children. Although the technical problems associated with HD in young infants are considerable, this modality in some instances can be successfully used in the infants with ESRD, especially those awaiting transplantation [36,17]. The use of chronically implanted venous catheters or the creation of arteriovenous fistulas in infants and young children have enabled pediatric nephrologists to successfully hemodialyze even very young infants.

Access for Dialysis Procedures

Hemodialysis (HD)

Achieving venous access in infants and young children has been challenging pediatricians, pediatric house officers, and pediatric surgeons for many years. The often very small size of the child, the small size/caliber of their veins and arteries, and, often, the lack of easily visible or palpable veins, together with the knowledge that, in many instances, children develop their renal insufficiency slowly and have required in the past multiple intravenous infusions of fluids or medications with resultant venous injury, scarring and thrombosis, makes the creation and maintenance of ade-

quate access both challenging, frustrating, and rewarding in these young patients.

In infants and children who are to be started on HD as their maintenance dialysis therapy, single and dual-lumen venous catheters, placed either percutaneously or surgically implanted, accounts for vascular access in about half of children on HD, with the remainder divided equally between arteriovenous fistulas and grafts [4]. The site most commonly used for acute vascular access for hemodialysis is the subclavian vein; however, it should be noted that long term or repeated use of the subclavian veins early in life may result in vessel scarring with impaired blood flow from the vein, which may limit the availability of the good venous drainage needed for the future creation of arteriovenous fistulas. The creation of arteriovenous fistulas in small children is an ongoing and often frustrating challenge for the surgeons (who may be vascular surgeons, plastic surgeons, hand surgeons, or pediatric surgeons) involved in the creation of this important source of chronic vascular access; the use of microscopes in the operating room have been used with very acceptable results in small children [63]. With the development and increased usage of tunneled intravenous (IV) access (both percutaneous and surgically placed) for a variety of vascular access needs in infants and young children, this type of access is becoming much more frequently utilized in infants and children requiring acute and chronic HD access [39]. These can be dual lumen catheters in many cases, although single lumen central venous access can be utilized with "single needle" adaptation in the hemodialysis procedure. Despite the increasing use of chronic PD as an initial modality in young children, HD remains an important tool in the treatment of acute and chronic renal failure in infants and children [11, 36].

Peritoneal Dialysis (PD)

The peritoneal access utilized most commonly in children are Tenckhoff curled catheters with single pre-peritoneal cuff-cuff and straight tunnels [80]. Most of these catheters are surgically implanted in the operating room; however, the percutaneous [44, 69] and peritoneoscopic placement [16] in children, while not widely utilized at present, are beginning to be used in children at some centers. When peritoneal catheters are used in young infants, attention should be given to placing the catheter exit site in a position to avoid fecal and urinary contamination [10]; most pediatric nephrologists prefer PD catheters having downward facing exit sites which seems to allow for less accumulation of extraneous material, and less irritation of the exit site area. In some instances, presternal placement of the peritoneal catheter and exit site has been advocated [66]; this may allow less fecal and urinary soiling of the catheter and fewer exit site infections.

Pediatric Dialysis Prescription

Hemodialysis (HD)

The initiation of chronic HD in an infant or young child should of course be performed under carefully controlled circumstances, with close and frequent monitoring of vital signs, blood pressure, physical examination, and assessment of body weight before, during (if available, with in-bed scales) and after HD treatments. With the use of pediatric catheters, small hemodialyzers, and smaller volume blood lines, the extracorporeal blood volume

can often be maintained at < 8 – 10% of the intravascular volume. Blood flow rates generated by the dialysis peristaltic pump usually range from 3 – 5 mL/kg body weight/ minute, often starting at the lower blood flow rate and slowly increasing the rate during the procedure. Heparinization is provided during the HD procedure, typically with a pre-HD infusion of 10 – 20 U/kg/dose with bedside monitoring of the activated clotting time (ACT). The decision on the amount of ultrafiltration (fluid volume to be removed from the patient during the dialysis process) will depend on the extent of the pre-dialysis volume status (including the presence of edema), blood pressure, and the weight gain noted between dialysis procedures [10]. In young infants, careful attention to body temperature during HD is also warranted. The evaluation of hemoglobin, hematocrit, and iron stores is also warranted, since infants may loose a small amount of blood during each dialysis procedure. Monitoring these parameters should be an ongoing process so that the need for adjustments in medications (rHu-EPO and iron) is recognized.

Complications of Pediatric HD

The complications associated with infant and child HD include problems related to vascular access, including thrombosis, stenosis, and infection. Of these, thrombosis is the most common reason for loss of access to the child's circulation. Because of the smaller blood volume in children, hypotension during the HD treatment occurs more commonly than with adults. This requires close monitoring of vital signs, blood pressure, and body weight as well as closer attention to the patient by the HD staff during the treatment. Hypovolemia is often associated with tachycardia, muscle cramping, nausea, and vomiting. Prompt relief of these symptoms is achieved with rapid restoration of circulating volume with normal saline, 5% albumin, or mannitol. Muscle cramping may occur during the HD treatment, and may be related to hypovolemia, hypotension, and electrolyte shifts that may occur during dialysis. Treatments of cramping have included increasing the dialysate sodium concentration, administration of hypertonic saline or glucose during the cramping episode, and the use of oral quinine prior to dialysis if recurrent cramping occurs.

The dialysis dysequilibrium syndrome (DDS) occurs in children, with symptoms often resembling those of hypovolemia. The cause of DDS is not entirely clear, and may relate to the brisk lowering of serum osmolality that occurs during HD, with subsequent development of acute cerebral edema. Manifestations include headache, nausea, vomiting, blurred vision, restlessness and, in severe situations, significant mental status disturbances including disorientation and coma. DDS can usually be avoided by reducing the decrease in osmolality by shortening dialysis time and reducing blood flow rates. In situations where the patient's serum urea nitrogen level is quite high and HD is being initiated, the administration of 0.5 g/kg body weight of mannitol is useful in preventing intracellular fluid accumulation. After several HD treatments, with lowering of the serum urea nitrogen level, this therapeutic intervention is usually no longer needed.

Peritoneal Dialysis (PD)

The PD prescription will need to include the type of dialysis fluid to be instilled, the dex-

trose (or, occasionally, the amino acid) concentration of the instilled fluid, the volume of the instilled fluid, the length of time the dialysis fluid is allowed to dwell within the peritoneal cavity, and the amount of time allowed for drainage of the peritoneal fluid from the peritoneal cavity. Children on continuous ambulatory peritoneal dialysis (CAPD) will usually have commercially pre-filled dialysate "bags" which they will connect to their peritoneal catheter, instill, dwell for 3 – 6 hours, and then drain and instill new dialysate. These children will have a long dwell of dialysate in their peritoneal cavity for 8 to 10 hours overnight. Children on automated PD (APD) will connect (or be connected) to the dialysis infusion tubing at night, with the machine set to deliver, and dwell, a prescribed amount of dialysate. Typically, the nighttime cycles will be every 60 – 120 minutes; at the end of the procedure, before the child is removed from the automated cycler, a daytime dwell is often instilled in the child's peritoneal cavity.

Most of the APD devices currently used will record the amount of dialysate (plus ultrafiltrate) removed during the drainage cycle based on the weight of the drainage bag. The usual amount of dialysis fluid instilled on a chronic basis is 40 – 50 mL/kg body weight (~1100 mL/m^2 body surface area [BSA]) per infusion cycle. After a PD catheter is first inserted, the catheter is not used for several weeks to a month to allow fibrosis around the catheter to avoid dialysate leakage. If this waiting period is possible, the PD catheter should be flushed with very small volumes of heparinized PD fluid to maintain catheter patency and remove residual blood from the insertion procedure. When dialysis is started (whether immediately or after several weeks), low volumes of dialysate are instilled initially (between 10 – 20 mL/kg body weight), with gradually increasing volumes over 1 – 2 weeks, recognizing that the efficacy of dialysis and ultrafiltration will not be optimized until larger volumes of dialysate are used. In patients who need volume removal for the treatment of congestive heart failure, pulmonary edema, effusions, or edema, the use of dialysate solutions with higher dextrose concentrations (4.25% is the highest dextrose concentration commercially available) can be used. A substantial number of infants and children with ESRD requiring dialysis will have significant urine output, and the lower dextrose concentrations can be used (usually, 1.5% dextrose solutions). Often, a higher dextrose concentration solution is used during the longest dwell period (nighttime for patients on CAPD and daytime for those on APD).

Special attention is required for younger infants and children (especially those < 2 years of age) on PD. It has been clinically apparent that neonates and young infants absorb glucose from dialysate more rapidly that older children and adults. Peritoneal equilibration studies have demonstrated that children < 2 years of age transport glucose and creatinine more rapidly than children 3 – 14 years of age, and that children 3 – 14 years of age transport glucose more rapidly than adults [45]. Thus, in order to optimize the dialysis prescription for infants, a balance between shorter dwell times (optimizing ultrafiltration), longer dwell times (optimizing diffusion and thus blood purification) is required [22, 23, 11]. In some instances, the use of the peritoneal equilibration test (PET; modified for children) may assist in formulating an efficient peritoneal dialysis prescription.

Complications of PD

The major complications associated with PD include loss of PD catheter patency due to fibrin deposition or thrombosis withing the

lumen of the PD catheter, occlusion of the PD catheter with the peritoneum preventing inflow or outflow of dialysate (often associated with catheter migration or omental occlusion), and catheter-associated infection. Fibrin deposition or thrombosis is often treatable with the instillation of thrombolytic agents (e.g. urokinase). In addition, catheter infusion or drainage difficulty resulting from catheter migration is occasionally treatable with flouroscopic manipulation of the PD catheter. Infections in PD patients include infections of the catheter skin exit site ("exit site" infections), infections of the PD catheter tunnel, and peritonitis. Data from NAPRTCS show an episode of peritonitis occurring at the rate of one infection every 13.3 months, with the frequency higher in younger children [80].

The host factors involved in the genesis of peritonitis in children have recently been reviewed [12]. Prompt recognition of peritonitis, and prompt treatment, is certainly warranted; decreases in the peritoneal transport of creatinine has been seen using data from PETs in children with peritonitis [50]. Gram-positive organisms are responsible for a significant percentage of peritonitis and exit site/tunnel infections. Exit site infections remain an ongoing issue in the care of PD patients, and may progress to tunnel infections and peritonitis. Caudal positioning of the exit site, the use of chlorhexidine as a cleansing agent [35], and ongoing review of the care and recognition of exit site problems [55] is advisable. Loss of PD catheters due to peritoneal, tunnel, and exit site infections with *Pseudomonas*, *Staphylococcus*, and fungal infections remains a major cause of treatment failure in children on PD. When children on PD require systemic antibiotic therapy, the use of prophylactic oral anti-fungal agents do seem to decrease the subsequent development of fungal peritonitis.

Growth of Children on Dialysis

The impairment of linear growth in children with ESRD treated conservatively or with dialysis and transplantation remains an ongoing therapeutic challenge in both the physical and psychosocial habilitation of infants and children with renal disease. The etiology of growth retardation in children with CRF and ESRD is thought to be multifactorial and includes protein-calorie malnutrition (well described in children with CRF [7, 67], chronic acidosis [75], renal osteodystrophy [29], uremic toxins, and, more recently described, disturbances of the growth hormone (GH)/insulin-like growth factor (IGF) axis [74]. rhGH has been shown in multicentered placebo controlled studies to be effective in treating short children with preterminal CRF on conservative treatment [20]; children on dialysis also increase in height in response to rhGH, although their response tends to be less than those who received rhGH prior to dialysis [82]. After renal transplantation [43], growth is accelerated in growth-delayed children. In transplanted children who are pubertal, rhGH also increased linear growth [30].

The disturbances of the GH/IGF axis in infants and children with growth delay and CRF are currently undergoing active investigation. Plasma GH levels in children are usually normal or high, suggesting GH insensitivity in these children. Plasma GH binding protein concentrations are low in patients with CRF [53]. GH's somatotropic activity is mediated in part by stimulating the production of circulating IGF-1. IGF-1 levels are normal to somewhat decreased in children with CRF. In addition, IGF binding proteins (IGFBPs) are found in the circulation and are present in increased concentrations in children with

CRF. This increased concentration appears to be largely due to impaired renal filtration of low molecular weight proteins [72] and also to increased production of several of the binding proteins [73]. The increase in concentration of circulating IGFBPs will lower free IGF levels. Administration of GH increases IGF-1 levels and IGF bioactivity.

RhGH treatment has been shown to increase the growth velocity and the bone mineral density of children with CRF [37]. In general, children managed conservatively for their CRF respond better to rhGH the younger they are. After transplantation, young age, good allograft function, higher pretreatment growth velocity, and low steroid dose are associated with a better response to rhGH therapy [59]. A recent review of the clinical data suggests that the use of rhGH does not worsen or induce renal osteodystrophy in children with CRF; however, the risk of slipped capital femoral epiphysis and avascular necrosis of the femoral head have been reported in children with renal osteodystrophy and in rhGH-treated children; thus, complaints of bone pain, hip, knee, or gait disturbances should be evaluated aggressively [81]. Although rhGH does induce resistance to the actions of insulin, overt new-onset diabetes mellitus has not developed in children with CRF treated with rhGH [42]. Benign intracranial hypertension has been reported in some children receiving rhGH [40]; thus, regular fundoscopy and attention to headaches and blood pressure is clearly warranted in these children. Finally, the possibility that the increased body mass induced by rhGH may reduce renal function (perhaps by inducing glomerular hyperfiltration) has been examined; over a treatment period of 5 years, creatinine clearance decreased by merely 8 mL/minute/1.73 m^2 [21].

Hyperparathyroidism and Renal Osteodystrophy

Hyperparathyroidism is a well described finding in persons of all ages with CRF. Factors contributing to the development of high parathyroid hormone (PTH) levels in children with CRF include hypocalcemia, hyperphosphatemia, decreased production of activated vitamin D (calcitriol), and decreased clearance of circulating PTH from the circulation. The clinical manifestations of renal osteodystrophy in children may vary depending upon the age of onset of CRF, and includes skeletal deformities, bone pain, growth retardation, extraskeletal calcification, and muscular weakness. The frequency of skeletal deformities in children with CRF is related in part to the normally high rates of bone growth and skeletal remodeling that characterize the growing child. In young children, renal osteodystrophy often resembles vitamin D deficient rickets, with widening of the metaphysis beneath the growth plates of long bones (characterized by enlargement of the wrists and ankles), along with Harrison's grooves and rachitic rosary. Other clinical manifestations of renal osteodystrophy in children are found in Table 3.

Renal osteodystrophy has been shown to represent a spectrum of histopathologic conditions. The most clearly recognized is the "high-turnover" bone lesion osteitis fibrosa. In this lesion, elevated PTH levels result in increases in both osteoclastic and osteoblastic activity, with high rates of bone remodeling, and fibrous tissue found near bone trabeculae, within marrow space, or replacing individual trabeculae [60]. Recently, the prevalence of the "low turnover" bone lesion, termed adynamic or aplastic lesion, has been reported more frequently in the pediatric population.

Table 3. Clinical Manifestations of Renal Osteodystrophy and Secondary Hyperparathyroidism in Children

– Craniotabes
– Frontal bossing
– Enlargement of ankles and wrists
– Rachitic rosary
– Harrison's groove
– Genu valgum
– Slipped epiphyses (femoral)
– Dental abnormalities
– Soft tissue calcification
– Calciphylaxis
– Growth retardation

Osteomalacia is a primary histologic feature, with normal or reduced amounts of osteoid, reduced osteoblastic and osteoclastic activity, no tissue fibrosis, and low or unmeasurable bone formation [61]. Patients may also have histologic evidence of both osteomalacia and osteitis fibrosa, or, mild lesions of renal osteodystrophy, with mild increases in osteoclastic activity and no peritrabecular fibrosis [65].

The treatment modalities available for the prevention and treatment of secondary hyperparathyroidism and renal osteodystrophy in infants and children generally includes attempts to reduce the intestinal absorption of phosphorus (thus reducing hyperphosphatemia) and the administration of various vitamin D sterols. Low-phosphorus diets are generally unpalatable and compliance with this type of diet is quite difficult for children and their families. However, limitation of foods with high phosphorus contents may be somewhat helpful. Most children with CRF will require the use of oral phosphorus binding agents which, when taken with food, reduces intestinal absorption of phosphorus. Aluminum salts, widely used in the recent past, were effective phosphorus binding agents but were found to be associated with aluminum accumulation and resulting osteomalacia and encephalopathy [62, 49, 15]. Recently, calcium salts, most commonly calcium carbonate, have been used as phosphate binders. Liquid preparations of calcium carbonate are available for use in infants and young children unable to swallow tablets. The usual goal of therapy with phosphate binders is to maintain serum phosphorus levels in the mid to upper range of normal levels for age, and to avoid hypophosphatemia.

Several vitamin D sterols have been used to control the high turnover bone lesions of secondary hyperparathyroidism, osteitis fibrosa. The medications currently used include 1,25-dihydroxyvitamin D (calcitriol), dihydroxytachysterol (DHT), and 1-alpha-hydroxyvitamin D (alphacalcidol). A study comparing calcitriol with DHT showed these forms of vitamin D to be equally efficacious in controlling renal bone disease [13]; the cost of DHT is currently substantially lower than calcitriol. Calcitriol may be administered by the oral, intramuscular (IM) [14], IV, or intraperitoneal (IP) route [34]; currently, the only significant advantage to the non-oral forms of therapy with Vitamin D sterols is compliance. Intermittent calcitriol therapy has been found to be effective in reducing PTH levels and healing osteitis fibrosa; intermittent therapy is usually done 2 – 3 times weekly. While many centers are currently using oral calcium salts to bind phosphorus and intermittent oral, IV, or IP calcitriol to control osteitis fibrosa, this combination of therapies has been implicated in the apparently increasing incidence of low turnover adynamic bone disease [25]. Currently, it seems reasonable to maintain a level of intact PTH in a range 2 – 4 times the upper level of normal, and to maintain serum calcium levels within the up-

per ranges of normal. It should be understood that the long-term implications of adynamic bone disease in young children are uncertain.

Anemia

The majority of infants and children with CRF will develop a normochromic, normocytic anemia primarily due to reduced production of erythropoietin (as reflected by reduced serum levels) for the degree of anemia. In addition, other uremic toxins have been implicated in the anemia of CRF [41]. Several of the clinical features of uremia appear to be improved with the use of recombinant human erthyropoietin (rHu-EPO), suggesting that the symptoms may be due in part to the anemia of CRF. These symptoms include fatigue, cognitive dysfunction, cold intolerance, and sleep disturbances [79]. The use of rHu-EPO has been shown to improve cardiac function and exercise tolerance, and also results in subjective improvements in physical performance, health, and school attendance [47, 48]. rHuEPO is not effective in patients with significant iron deficiency [77]. Most children with CRF and anemia will be placed on oral iron therapy in preparation for or during therapy with rHu-EPO. In situations where oral iron administration is not sufficient to achieve iron stores needed for erythropoiesis, IV iron dextran has been used. Children on HD will typically receive rHu-EPO 3 times a week intravenously at the conclusion of their dialysis session, usually beginning with a dose of 50 U/kg body weight per treatment. The subcutaneous administration of rHu-EPO once or twice a week has been shown to be an effective modality for maintaining hemoglobin and hematocrit values in children on PD [46, 57; 68, 51]. In addition, children on PD have been shown to have an effective erythropoiesis receiving rHu-EPO in doses of 100 – 300 units IP given once or twice a week during a long (12 hour) dwell period [58, 70]. The major adverse effects that have been noted in children treated with rHu-EPO has been iron deficiency and hypertension, either exacerbation or de novo. Both of these effects are usually readily managed [32].

Cardiovascular Function and ESRD in Children

Cardiovascular complications of ESRD are not infrequent in children; data from the European Dialysis and Transplant Association have suggested that > 40% of deaths in children < 15 years of age could be attributed to cardiovascular causes [9], with only 17% of the deaths associated with hyperkalemia-induced dysrhythmias. Left ventricular (LV) abnormalities, particularly LV hypertrophy and increased LV mass, have been found in a significant number of children with CRF, patients on PD and HD, and in those children who have had received renal transplants [33]. The causes of these LV abnormalities is probably multifactorial and includes hypertension (a well-known cause of concentric LV hypertrophy), anemia [47], and, possibly, an as yet undefined effect of uremia. [76]. In addition, diastolic dysfunction has been noted in children receiving either PD or HD [26]. Hyperlipidemia has also been found in children receiving either HD [52], PD [56], and those who have undergone renal transplantation [64]. Considering the increasingly long-term survival of infants and children with CRF, assessment of cardiac structure and function by periodic echocardiography, correction of those factors amenable to correction, includ-

ing anemia, hypertension (including the use of home blood pressure and ambulatory blood pressure monitoring), and obesity, as well as on-going studies on the relative risk/benefits of attempts to ameliorate hyperlipidemia, seems prudent.

Nutritional Issues in Infants

Young patients with CRF are at significant risk for protein-calorie malnutrition. Children (especially infants) will often have reduced appetites, gastroesophogeal reflux, vomiting, and delayed gastric emptying, all of which can limit intake of calories and nutrients. Optimal or improved nutrition improves growth [1] and may improve the neurodevelopmental potential in uremic infants [18]. Many children with the onset of ESRD before 2 years of age will require supplemental calories via tube feedings using overnight nasogastric tube feedings or gastrostomy tube placement. However, tube feeding (nasogastric or gastrostomy) may be associated with vomiting and aspiration. Children who start nasogastric tube feedings during the first year of life may also develop feeding dysfunction after the tube feedings have been discontinued, with difficulty noted in chewing and swallowing [71]. Significant protein losses via dialysate in children on peritoneal dialysis have been noted, with losses in infants nearly 2-fold greater compared with older children and adults (when measured as protein losses/m^2 BSA) [55]. The use of amino acid solutions incorporated within the dialysate as the osmotic agent may help to prevent amino acid/protein losses and improve the infant or child's overall nutritional status [6]. Of course assuring the appropriate ingestion of essential vitamins, especially water-soluble vitamins, is required; limiting the intake of the fat-soluble vitamin A may also be required.

Psychosocial Considerations of Dialysis in Infants and Children

CRF and dialysis modalities have a significant and ongoing impact on the psychologic and social well being of children with ESRD and their families. Children will often have major concerns about their physical appearance and the differences between themselves and their peers. Certainly, those with poor growth, episodic edema, Cushingoid facies, external HD or PD catheters, arteriovenous fistulas, and multiple surgical scars may result in features such as low self-esteem, increased anxiety, anger, and behavioral disturbances [24]. In addition, outpatient clinic visits and hospitalizations for illnesses and procedures often require the child to miss school (and the parents to miss work). The response of the parents to the multiple tasks required in the care of these children (including administration of multiple medications, monitoring the child's diet, setting up and performing dialysis for children on home dialysis, or transporting the child for center-based dialysis) can create significant parental relationship problems, anxiety, depression, and parental "burn-out" [38]. Recent reports have suggested that poor adherence to treatment is associated with measures of poor adjustment to diagnoses and dialysis by children and parents, higher self-ratings of anxiety and depression in children and parents, lower family socioeconomic status, and increasing age (younger children had better adherence to therapies than adolescents [8]. Clearly, the availability of psy-

chosocial support of varying types from the dialysis care team is an extremely important process in the therapy for these children and their families.

Conclusions

CRF and ESRD in infants and children remains a major challenge for all of the persons involved in the care of these children. Attempting to adjust the administration of medications and dialysis therapies in order to allow these children to go to school, interact with peers, and achieve as much "normalcy" in their lives as is reasonable, should certainly be a major goal of health care providers and families of these children, while at the same time optimizing the dialysis, medication, and nutritional prescription. In most children, the goal of dialysis therapies is to maintain the patient in as healthy a condition as possible until renal transplantation can be performed.

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